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Conference on Gastric Cancer

FRIDAY MORNING SESSION

OCTOBER 11, 1940

A CONFERENCE on gastric cancer was held October 11 and 12, 1940, under the auspices of the National Advisory Cancer Council, in the auditorium of the Administration Building, National Institute of Health, Bethesda, Md. Following is a list of the members of the Gastric Cancer Conference:

Alvarez, Dr. Walter (Mayo Clinic)
Anderson, Dr. Rudolph (Yale University)
Bayne-Jones, Dr. Stanhope (Yale University)
Brunschwig, Dr. Alexander (University of Chicago)
Collins, Dr. S. D. (National Institute of Health)
Compton, Dr. Arthur H. (University of Chicago)
Conant, Dr. James B. (Harvard University)
Cooper, Dr. W. A. (New York Hospital)
Cowdry, Dr. Edmund V. (Barnard Free Skin and Cancer Hospital)
Crowell, Dr. Bowman C. (American College of Surgeons)
Cutler, Dr. Max (Chicago Tumor Institute)
Dochez, Dr. A. R. (Columbia University)
Dublin, Dr. Louis I. (Metropolitan Life Insurance Co.)
Evans, Dr. Lester J. (Commonwealth Fund)
Ewing, Dr. James (Memorial Hospital)
Gardner, Dr. W. U. (Yale University)
Griffith, Dr. Charles M. (Veterans' Administration)
Harrison, Dr. Ross G. (Osborne Zoological Laboratory)
Hektoen, Dr. Ludvig (Executive Director, National Advisory Cancer Council)
Hollander, Dr. Franklin (Mount Sinai Hospital, New York)
Holmes, Dr. George W. (Harvard University)
Ivy, Dr. A. C. (Northwestern University)
Little, Dr. C. C. (Roscoe B. Jackson Memorial Laboratory)
Long, Dr. Perrin H. (Johns Hopkins University Medical School)
Lorenz, Dr. Egon (National Cancer Institute)
McKittrick, Dr. Leland S. (Palmer Memorial Hospital)
McNeer, Dr. Gordon (Memorial Hospital)
Macklin, Dr. Madge Thurlow (University of Western Ontario)
Mallory, Dr. Tracy B. (Massachusetts General Hospital)
Marshall, Dr. Samuel F. (Lahey Clinic)
Middleton, Dr. William S. (University of Wisconsin)
Moe, Mr. Henry Allen (John S. Guggenheim Foundation)
Morton, Dr. John J. (University of Rochester)
Murphy, Dr. James B. (Rockefeller Institute for Medical Research)
O'Brien, Dr. Joseph (University of Buffalo)
Oughterson, Dr. A. W. (Yale University)
Pack, Dr. George T. (Memorial Hospital)
Parran, Dr. Thomas (Surgeon General, Public Health Service, Chairman)
Reid, Dr. Mont R. (University of Cincinnati)
Rhoads, Dr. C. P. (Memorial Hospital)
Rous, Dr. Peyton (Rockefeller Institute for Medical Research)
Rusch, Dr. H. P. (University of Wisconsin)
Schiff, Dr. Leon (University of Cincinnati)
Schindler, Dr. Rudolf (University of Chicago)
Schram, Dr. Mildred (International Cancer Research Foundation)
Shear, Dr. M. J. (National Cancer Institute)
Smith, Dr. George M. (Yale University)
Spencer, Dr. R. R. (Assistant Chief, National Cancer Institute)
Stewart, Dr. H. L. (National Cancer Institute)
Tannenbaum, Dr. Albert (Michael Reese Hospital)
Thompson, Dr. L. R. (Director, National Institute of Health)
Turner, Dr. Joseph C. (Presbyterian Hospital)
Voegtlin, Dr. Carl (Chief, National Cancer Institute)
Walters, Dr. Waltman (Mayo Foundation)
Warren, Dr. Shields (Harvard University)
Winternitz, Dr. Milton C. (Yale University)
Wood, Dr. Francis C. (St. Luke's Hospital)
Woods, Dr. Archie S. (John and Mary R. Markle Fund)
Zinninger, Dr. Max (University of Cincinnati)

The first session was called to order at 9:40 a. m., Friday, October 11, by Dr. Thomas Parran, the Chairman of the National Advisory Cancer Council.

Chairman Parran: Gentlemen: It is my very great pleasure and privilege this morning to welcome you here for this Conference on Gastric Cancer. We deeply appreciate the sacrifice which I know all of you have made during these busy days to come here and counsel with us concerning the several aspects of this very important problem.

Unique among the laws of our country is the act which established the National Cancer Institute. For the first time, definite provision is made in the Federal law for grants-in-aid by the Federal Government as a continuing national policy, in an effort to discover effective methods of prevention and control of a disease. Under the provisions of this law, the Public Health Service is authorized, yes, is directed, in cooperation with the National Advisory Cancer Council, to conduct, assist, and foster researches, investigations, experiments, and studies relating to the cause, prevention, and methods of diagnosis and treatment of cancer, and to promote the coordination of researches conducted by the Institute and similar researches conducted by other organizations and agencies.

Pursuant to these provisions of law, to this intent of the Congress, the National Advisory Cancer Council has given considerable thought to ways by which we can bring about a greater degree of coordination of effort, having in mind that the total of our several efforts may be greater than some of its individual parts.

It seemed to us that the subject of gastric cancer, which represents such a baffling problem and which accounts for about 20 percent of the total mortality from the disease, would be the most profitable subject for this initial discussion.

I believe this gathering is unique in the history of cancer investigations, because for the first time representatives of the various groups, the internists, the radiologists, the surgeons, the pathologists, and the cancer investigators, have been brought here in the hope that out of this conference will come some definite plans and projects for cooperative research.

We have long recognized the need of studying human cancer as well as induced cancer, experimental cancer in the laboratory. In other words, it has seemed to us that the laboratory investigator and the clinician can very profitably come together.

Finally, I should like to say that if we are successful in this major objective of this conference, the conference will have importance far beyond the subject of gastric cancer itself. It will have a significance, it seems to me, in other fields of research, some of which are most urgently and directly related to our current problems of national defense.

The responsibility for this meeting fell primarily upon a member of the National Advisory Cancer Council, Dr. George M. Smith, and I am going to ask Dr. Smith if he will preside this morning. I hope also at later sessions that the director of the National Cancer Institute, Dr. Voegtlin, will preside, Dr. Hektoen likewise, and Dr. Murphy.

Dr. Smith, will you take the chair?

Chairman Smith: The first subject to be discussed is the Trend and Geographic Variation in Cancer Mortality and Prevalence, with Special Reference to Gastric Cancer. Dr. S. D. Collins, principal statistician, National Institute of Health, United States Public Health Service, will present the paper.

Trend and Geographic Variation in Cancer Mortality and Prevalence, With Special Reference to Gastric Cancer[1]

By SELWYN D. COLLINS, *principal statistician*, MARY GOVER, *associate statistician*, and HAROLD F. DORN, *senior statistician, Public Health Methods, National Institute of Health, United States Public Health Service*

This paper summarizes briefly and in graphic form the results of certain statistical studies of cancer, with special reference to gastric cancer. These studies by the United States Public Health Service pertain to (1) the trend of cancer mortality (a) since 1900 in the 10 States and the District of Columbia for which records are available, and (b) since 1920 in different geographic areas; (2) the variation from State to State in cancer mortality in 1930–32; and (3) the prevalence of cancer cases under treatment in 12 urban areas classified into three geographic regions.[2]

TREND OF CANCER MORTALITY

Cancer mortality is necessarily based on recorded deaths and consequently is subject to some errors of diagnosis. The rates presented under mortality in this paper are not subject to the error due to varying age distribution because all rates for all ages have been adjusted to a standard age distribution.

Considering mortality from all cancer, the rate (adjusted) in the registration States of 1900 has been rising more rapidly among males than females (fig. 1), so that in 1935 the male rate was 87 percent of the female rate as compared with 59 percent in 1900. The recorded death rate from cancer of the stomach and liver rose rather rapidly in both sexes from 1900 to 1915, and in males the rise continued until about 1922. Since 1922 the recorded rate for females has shown a definite decline, but the rate for males has declined only slightly. Cancer of the peritoneum, intestines, and rectum has increased steadily throughout the period 1900–1935; among females, however, the rate of increase has been less since about 1920—that is, there is a tendency toward a flattening of the curve. Prior to 1930 cancer-mortality tabulations for the United States were made for only seven sites, and the above two are the only gastrointestinal sites available for trends during those years.

Considering mortality trends among persons of specific ages, the recorded rates for cancer of the stomach and liver (fig. 2) for males 25–34 and 35–44 years of age show definite declines since about 1923, and the rate at 45–54 has been practically level. Above 55 years, and particularly in the two oldest age groups (75–84, and 85 and over), the rise has been continuous since 1900. Among females (fig. 3) the decline since about 1920 has been more rapid and has included the age groups up to 75 years, although the decline at 65–74 was small. The two oldest age groups have risen continuously, but at a somewhat lower rate since 1920.

[1] *From the Division of Public Health Methods in cooperation with the National Cancer Institute, National Institute of Health.*

[2] *The full details of the mortality studies are given elsewhere (1–4), and the prevalence studies are being published in a series of articles in Public Health Reports (5–11).*

Since 1930 cancers of the stomach and of the liver have been tabulated separately. Deaths reported as cancer of the liver make up about one-fifth of the total for stomach and liver for males and about one-third of that for females. The trends since 1930 for cancer of the stomach are approximately the same as has been described for the two sites combined.

Cancer of the peritoneum, intestines, and rectum has shown a continuous rise in every age group for both males and females from 1900 to 1935. However, at the younger ages for males and in practically every age group for females, the rate of increase has been definitely less since about 1920 than prior to that time.

It should be remembered that the foregoing discussion of trends since 1900 pertains only to a small section (chiefly in the Northeast) of the United States encompassed in the death-registration States of 1900—the six New England States, New York, New Jersey, District of Columbia, Indiana, and Michigan. By 1920 a much larger number of States had been admitted to the registration area, and the trend of the recorded cancer mortality since that time can be examined in different geographic regions of the United States. The five regions are the Northeast, East North Central, South, West Central, and Pacific. In four of the five regions the death rate from cancer of the stomach and liver among males has shown a moderate decrease since about 1922, but in the South the curve has been about level since 1922 (fig. 4). Among females a decrease has occurred in the same four geographic regions, but it has been more rapid than among males. The South again is an exception with little decrease for females.[3] Cancer of the peritoneum, intestines, and rectum among males has increased at approximately the same rate in all five regions. Among females the increase in the South has been a little greater than in the other regions.

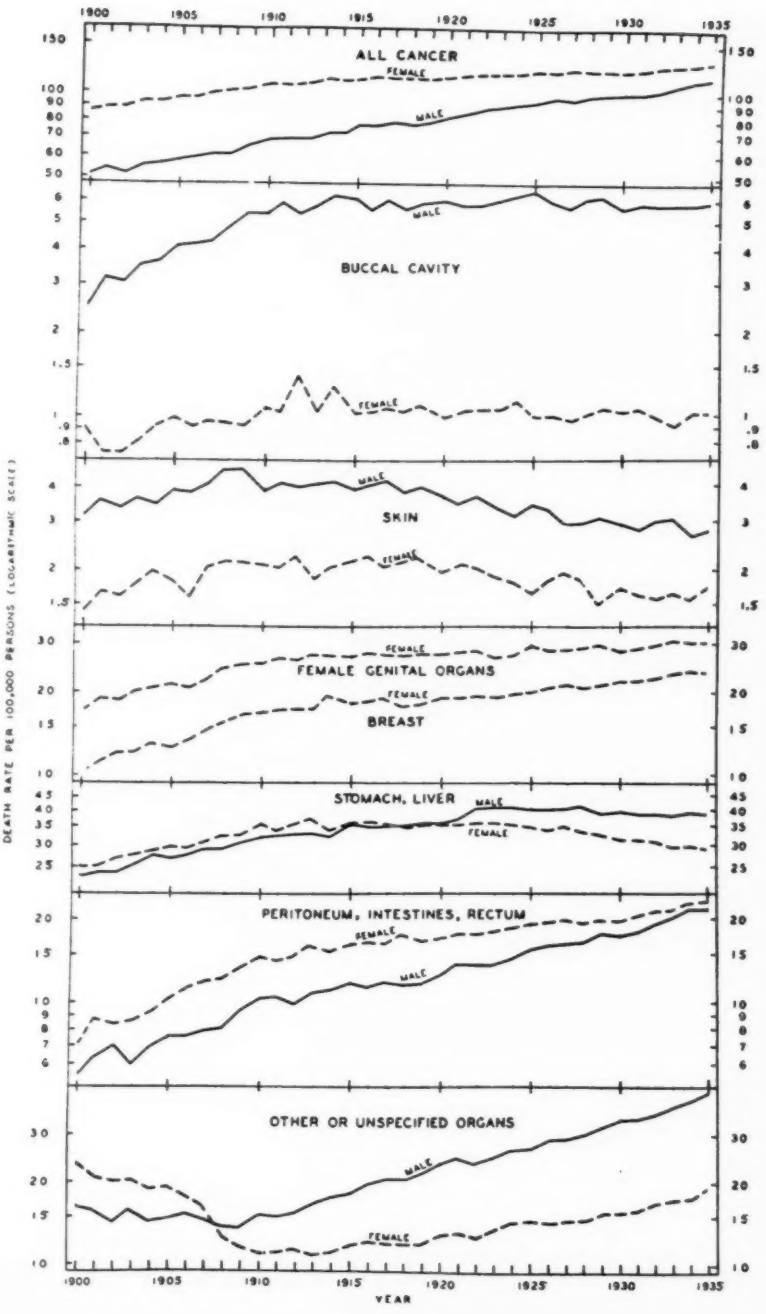
GEOGRAPHIC VARIATION IN CANCER MORTALITY

Since 1930 cancer mortality has been tabulated for 28 sites for males and females, the sites being the same except for the male and female genital organs. Data of this kind are available since 1930 for all States except Texas, which came into the registration area in 1933. Among males four of the five cancer sites with the highest mortality rates are gastrointestinal, the third important site, prostate, being the only one of the five that is not in the digestive system. Among females, cancer of the uterus and of the breast are the most important, but the next four sites are gastrointestinal.

The mortality rate from all cancer is definitely higher in the Northeast, East North Central, and Pacific regions. The South and the rural Plains and Mountain States of the West North and South Central regions have lower rates. Some of the excess in the recorded cancer death rates in the North and in the Pacific States may be due to better facilities for diagnosis, but the fact that various sites of

[3] *These trends are based on white and colored combined. Except in the South the number of Negroes is not great enough to influence the trend. In the South the trends for both white males and white females are about the same as described for white and colored combined.*

FIGURE 1.—Trend of mortality from cancer of different sites among males and females in the registration States of 1900, for the period 1900–1935. (Rates adjusted to the age distribution of the population of the United States in 1930. Registration States of 1900 were Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, District of Columbia, Indiana, and Michigan.)


1900
1905
1910
1915
1920
1925
1930
1935
ALL CANCER
FEMALE
MALE
BUCCAL CAVITY
MALE
FEMALE
SKIN
MALE
FEMALE
FEMALE GENITAL ORGANS
FEMALE
BREAST
FEMALE
STOMACH, LIVER
MALE
FEMALE
PERITONEUM, INTESTINES, RECTUM
FEMALE
MALE
OTHER OR UNSPECIFIED ORGANS
MALE
FEMALE
DEATH RATE PER 100,000 PERSONS (LOGARITHMIC SCALE)
YEAR

cancer show different kinds of variation suggests that some geographic differences are real and cannot be explained by the accessibility of the site of the cancer.

Another possible error which arises from the method of tabulating the data is that the rates are based on the place of death and not on place of residence of the patient. Therefore, if many patients from some States die in other States where more extensive cancer-treatment facilities are available, the death rates will be higher in these treatment centers. Beginning in 1937, deaths from some causes in the United States have been tabulated by residence of the patient rather than the place of his death; and in 1935 such a tabulation was made on an experimental basis. Although there is considerable change in the rates when they are thus corrected for residence, the general picture of higher rates in the Northeast, East North Central, and Pacific regions is not changed. Correction for residence is very important when comparing urban with rural areas, but there is not so much difference between whole States. The great majority of the State rates are changed less than 5 percent by correction for residence, but a few rural States (Nevada, Idaho, Wyoming, and North Dakota in 1935) are increased more than 10 percent.

The upper half of figure 5 shows the variation from State to State in death rates from cancer of the stomach and duodenum. The 12 States with the

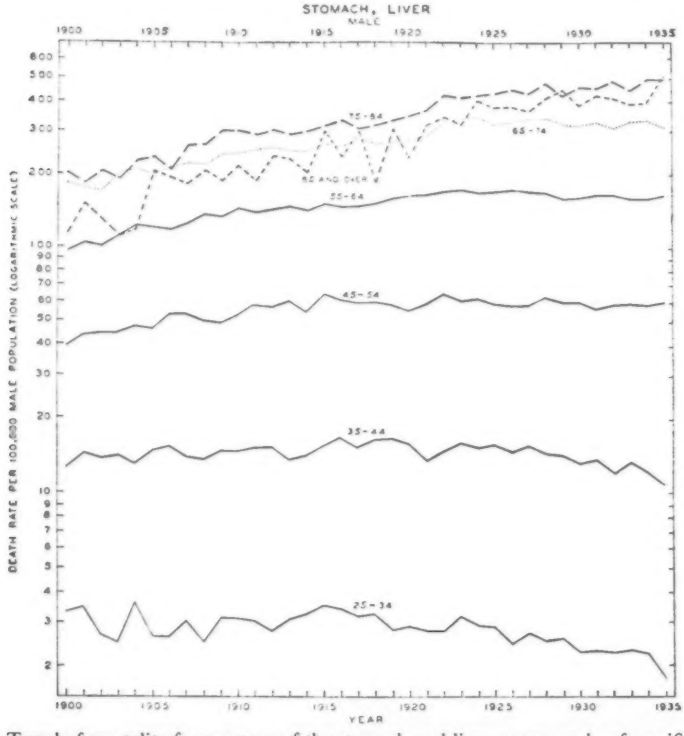


FIGURE 2.—Trend of mortality from cancer of the stomach and liver among *males* of specific ages in the registration States of 1900, for the period 1900–1935. (See fig. 1 for registration States of 1900.)

highest rates are black and the 11 with the lowest rates are white; the intervening States are hatched with heavy lines if they are above the average (median) and with light lines if below. Thus the darker the area, the higher the rate. It is seen that the high death rates from cancer of the stomach and duodenum are largely in the North and that every Southern State is among the lowest half and most of them among the lowest quarter of the States. The high northern belt extends, with few exceptions, from the Atlantic to the Pacific.

An examination of various sites of gastrointestinal cancer, including stomach and duodenum, liver, intestines, rectum, pancreas, and esophagus shows that they all have the same general distribution, with high rates in the Northeast, East North Central, and Pacific regions, and low rates in the South. There are some differences with respect to the Plains and Mountain States included in the West North and South Central regions; cancer of the stomach, esophagus, and pancreas all tend to be high at least in the northern half of these States, but rates for cancer of the intestines and rectum are not so high.

It will be of interest to compare this geographic distribution for gastrointestinal cancer with distributions for some other sites. The site with an outstandingly different geographic picture is skin cancer (lower half of figure 5), which is high throughout the South and low in the North

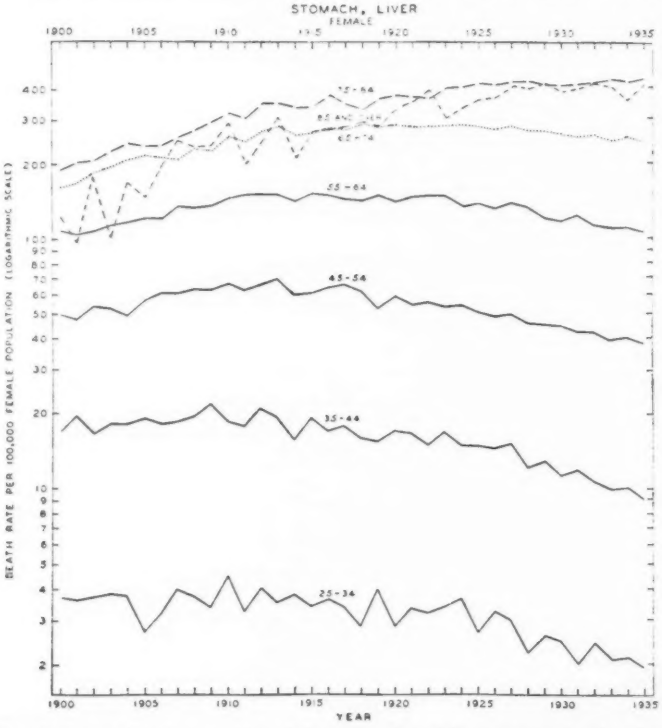


FIGURE 3.—Trend of mortality from cancer of the stomach and liver among *females* of specific ages in the registration States of 1900, for the peri d 1900–1935. (See fig. 1 for registration States of 1900.)

and in much of the West. Every State south of the southern boundary of Virginia, Kentucky, Missouri, and Kansas, and from Texas to the Atlantic, is among the 12 with the highest rates; Kentucky and Indiana are the only other States in this high group. This high skin-cancer rate in the South has been attributed to irritation resulting from excessive exposure to the sun.

The only other site with this peculiarly southern distribution is cancer of the pharynx and buccal cavity (except lip and jaw) among females. Here, as in the case of skin cancer, the Southern States are uniformly among the 12 States with the highest rates. Among males, however, the mortality in the Northern States is as high as, or higher than in the Southern States. In all geographic comparisons rates for the Southern States are based on the white population only.

Cancer of the breast should be mentioned as an important accessible site of cancer with a low mortality throughout the South; it thus resembles in geographic distribution the inaccessible digestive sites. Cancer of the uterus, however, is about as high in the South as in the North.

Data are available for the year 1935 which makes it possible to compute cancer death rates by size of city for each geographic section, with correction for residence of the patient. Data for cities under 10,000 and rural areas, cities 10,000 to 100,000, and cities over 100,000 in population indicate a wide difference in the total cancer death rate between large cities and rural areas. The middle-sized cities lie consistently between the two extremes.

Data are not available to compute death rates of this kind for cancer of specific sites. However, if cancer death rates in the different States are correlated with the percentage of the population which lives in urban areas (cities of 10,000 or more population in 1930), the following sites show a significant positive correlation: stomach and duodenum; esophagus; intestines, rectum, and anus; respiratory system; male

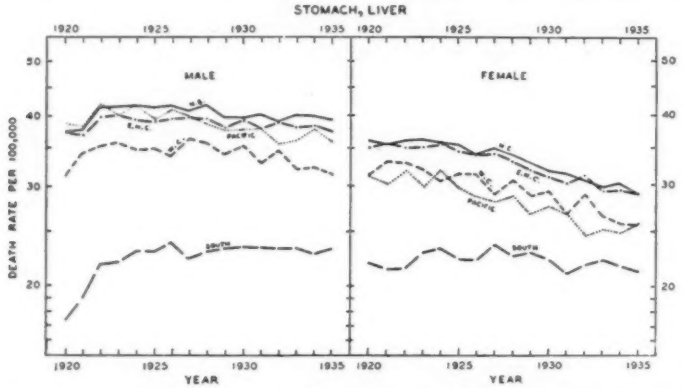


FIGURE 4.—Trend of mortality from cancer of the stomach and liver in different geographic regions of the registration States of 1920, for the period 1920–35. (Rates adjusted to the age distribution of the population of the United States in 1930. Registration States of 1920 were: *Northeast:* Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, Pennsylvania, New Jersey, Delaware, Maryland, District of Columbia; *East North Central:* Ohio, Indiana, Michigan, Illinois, Wisconsin, Minnesota, Missouri; *South:* Virginia, North Carolina, South Carolina, Kentucky, Tennessee, Mississippi, Louisiana, Florida; *West Central:* Kansas, Nebraska, Colorado, Utah, Montana; *Pacific:* California, Oregon, Washington.)

genital; female genital; and breast. The sites for which the correlations are not statistically significant are skin, for both males and females, and buccal cavity for females. Since the South is largely rural and usually has low rates, the Southern States were excluded, and these correlations recomputed for the 35 other States. Although the correlations were lower than for all States, they were statistically significant except for the sites noted above and for stomach and duodenum for both males and females.

Since cities have more facilities for the

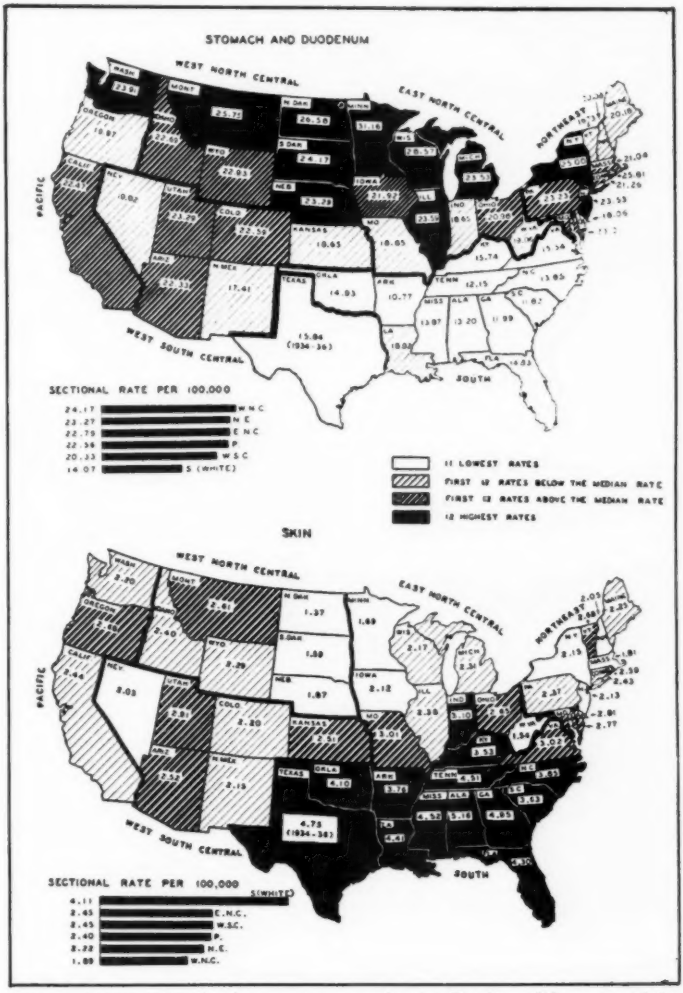


FIGURE 5.—Geographic variation in the average annual mortality from (1) cancer of the stomach and duodenum, and (2) cancer of the skin, in continental United States, 1930–32. (Rates adjusted to the age distribution of the population of the United States in 1930. For the South, including Texas, rates are based on the white population; elsewhere rates are based on the total population.)

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diagnosis and treatment of cancer and would draw patients from the rural areas, some method was sought to eliminate this factor. Data are available for the year 1936 for each State on the percentage of cancer deaths that occurred in hospitals. As might be expected, the percentage of deaths in hospitals is rather highly correlated with the percentage of the population that is urban. However, when partial correlation coefficients are computed, holding constant the percentage of cancer deaths that occurred in hospitals, the positive correlation of the cancer death rate with the percentage of the population that is urban persists for all cancer and for the four sites for which these kinds of data are available, namely, digestive tract, female genital organs, breast, and all other sites.

PREVALENCE OF CANCER AS INDICATED BY SPECIAL SURVEYS OF CASES UNDER TREATMENT

Special surveys of cancer prevalence were made in 12 cities in various parts of the country; the surrounding counties were included with the large city which was the nucleus of the area. The procedure was to compile as complete a list as possible of all doctors, clinics, and hospitals within the surveyed area from the American Medical Association Directory of Physicians, local telephone directories, and other sources. Each physician, clinic, and hospital was asked to report by name and address the cancer cases under treatment or observation at any time during the preceding calendar year; the year covered varied from 1937 in Atlanta to 1939 in Denver. Cancer is so frequently referred to specialists and hospitalized that reports from different doctors and hospitals included many duplicate cases which could be eliminated only by name and address. Moreover, the separation of nonresident from resident cases was possible only on the basis of the patient's address.

A temporary local office was set up in each city, and the telephone number and name of the person in charge were put on the letters which accompanied the questionnaires to the doctors. Thus additional explanation or information could be secured by telephone. It should be understood, however, that the survey did not end with a schedule from such doctors as made the return in response to the first request. The Public Health Service representative followed up the questionnaire with personal visits until returns were received from practically all physicians on the list. In the 12 areas surveyed there were 17,739 physicians, and returns were eventually obtained from 98 percent of them. Data were obtained from all of the 732 hospitals, clinics, and nursing homes except 6 of the latter.

The completeness of a return from a given physician would depend upon the completeness and accuracy of his records or, in many cases where no records were kept, upon his memory. In view of the seriousness of cancer and the few cases which would come to the attention of the average general practitioner during a 12-month period, it is believed that reasonably complete reports were secured in spite of the paucity of records of many doctors. Specialists, hospitals, and clinics usually have more complete records of patients treated, and in many instances clerical help to assemble the data was furnished by the Public Health Service. A considerable number of cancer deaths for the survey year that were not reported by the physicians were reported to the Public Health Service representative by the local registrar of births and deaths. However, many of these were persons seen for the first time in the last stages of the disease just

before death, and the physician did not consider them as his patients.

A survey of this kind would not yield accurate data for a common disease that is usually treated by general practitioners. Records kept by many doctors are scanty, and memory fails unless the case is unusual. In the case of cancer, 60 percent of all of the doctors had no cases and another 25 percent had only one or two. Thus the bulk of the cases were in charge of hospitals, clinics, and specialists, and the records were usually adequate.

The data from these surveys make it possible to compare cases and deaths with respect to site distribution and also with respect to geographic differences. Cancer cases as here used refer to those under treatment at some time during the study year, and both cases and deaths include only residents of the surveyed areas. Site refers always to the primary site. The surveyed cities and their geographic classification were: *North:* Chicago, Pittsburgh, Detroit, and Philadelphia, with an estimated white population [4] of 8,643,000 in the cities and surrounding surveyed counties. *South:* Atlanta, Birmingham, New Orleans, Dallas, and Fort Worth, with an estimated white population of 1,507,000 in the cities and surrounding surveyed counties. *West:* San Francisco, Oakland, and Denver, with an estimated white population of 1,385,000 in the cities and surrounding surveyed counties. Preliminary analyses for each city indicated that these groupings put similar cities together. All geographic comparisons relate to white persons in these three regions.

Number of Living Persons with Cancer as Compared With Annual Deaths

Bigelow and Lombard (*12, p. 100*) in cancer studies in Massachusetts estimated that there were 2 living persons with cancer for each annual death from that disease. Considering all 12 areas studied by the United States Public Health Service, there were 2.5 persons under treatment for each death during the year. In the northern cities, which would more nearly approximate conditions in Massachusetts, there were 2.3 cases per death (fig. 6). However, in southern cities there were 4.0, and in the West 2.8 cases per death.[5] The difference between the North and the South reflects to a considerable extent the excessively high skin cancer rates in the South. Considering all areas (fig. 7), there were 24 cases of skin cancer per death from that cause, 5 cases of buccal-cavity cancer, and 4 of cancer of the breast, as compared with only 1.4 cases per death for cancer of the digestive system.

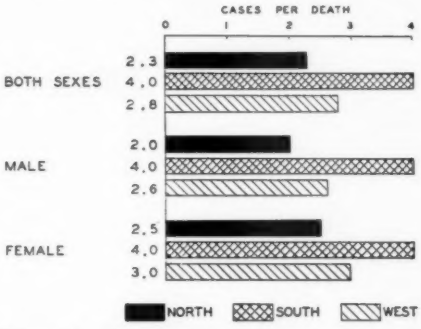


FIGURE 6.—Cancer cases under treatment at some time during the survey year per cancer death during the year, in surveyed cities of three geographic regions—12 large cities and surrounding counties, 1937–39. (Cases and deaths refer to white persons only. Number of deaths: North, male 5,245, and female, 5,507; South, male 641, and female, 820; West, male, 989, and female, 1,107.)

[4] *Population estimates based on 1930 and provisional results of 1940 census.*

[5] *In the present paper, cases refer to those under treatment at some time during the survey year, exclusive of those apparent cures that were under observation but were not under treatment. The inclusion of the cases under observation only would increase the ratios considerably. It is not entirely clear which standard was used in the Massachusetts estimates.*

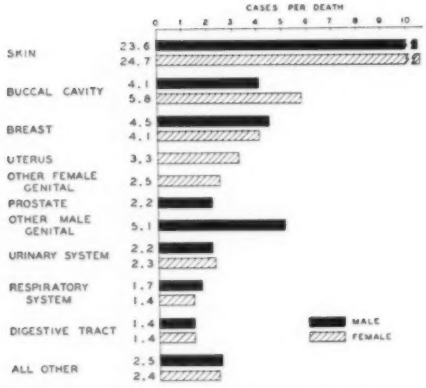


FIGURE 7.—Cases of cancer of certain sites under treatment at some time during the survey year per death from cancer of the same site during the year—12 large surveyed cities and surrounding counties, 1937–39. (Site refers to primary site; cases and deaths refer to white persons only.)

The contrast between cases and deaths is illustrated also by the site distribution of cases as compared with deaths (fig. 8). The deaths as well as the cases here referred to are those for the surveyed areas.

For males in all cities combined digestive-tract cancer constituted 34 percent of the total cases but 54 percent of the total deaths. At the other extreme, skin cancer constituted 18 percent of the cases but only 2 percent of the deaths. Among females digestive-tract cancer constituted 20 percent of the cases and 40 percent of the deaths, whereas skin cancer constituted 11 percent of the cases and 1 percent of the deaths.

CANCER PREVALENCE RATES

For all surveyed areas combined there were 313 white resident cancer patients under treatment at some time during the year per 100,000 population. The resident cancer death rate (no adjustment for age) in the surveyed areas was 124 per 100,000 during the survey year, as compared with a resident cancer death rate of 127 in 1935 for all cities in the United States with a population of 100,000 or over in 1930. The rates in the three regions are given in table 1.

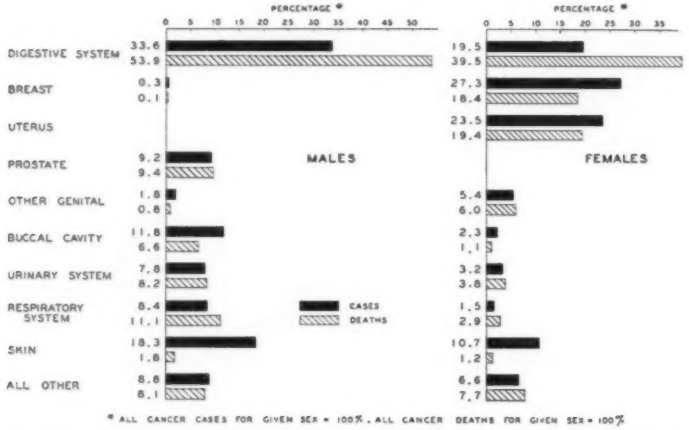


FIGURE 8.—Percentage distribution of cancer cases under treatment and of cancer deaths according to primary site, by sex—12 large surveyed cities and surrounding counties, 1937–39. (Numbers for all cancer: Cases, males 15,617, females 20,452; deaths, males 6,875, females 7,434.)

TABLE 1.—*Crude resident rates for all cancer among white persons in three regions of the United States*

Region	Case prevalence rate per 100,000 surveyed population	Annual death rate per 100,000 population	
		Surveyed area	All cities over 100,000
All	313	124	127
North	282	124	126
South	386	97	99
West	425	151	143

A comparison of the death rates [6] in the surveyed cities with those in all cities over 100,000 in the same region indicates close correspondence between the two sets of mortality data. Although none of these rates are adjusted for age differences, the comparisons within regions should be valid. Case and death rates for the surveyed areas cannot be adjusted until census populations are available by age. The death-rate adjustment for the 1935 data for all large cities suggests that the rates for the western surveyed areas would be considerably decreased by age adjustment, and both the North and the South would be moderately increased but probably not equalized.

The striking thing about these rates for all cancer is the low death rate and the high case rate in the South as compared with the North. Figure 9, which shows prevalence rates for different sites, gives an explanation for this apparent contradiction.

Cases of cancer of the digestive system in the North amounted to 79 per 100,000 population as compared with 58 in the South, but the West had a high rate of 109 per 100,000. When adjustment for age differences is possible, it will change the picture; but it is not probable that the North and South will be equalized. Crude rates for both males and females (fig. 10) maintain this same type of difference, digestive-tract cancer being lowest in the South, next in the North, and highest in the West. On the other hand, the South had a rate for breast cancer that was about the same as that for the North, and a rate for cancer of the uterus that was considerably in excess of that in the North and slightly in excess of that in the West. These statements are true for rates based on the female population (fig. 10) as well as for rates based on the total population (fig. 9).

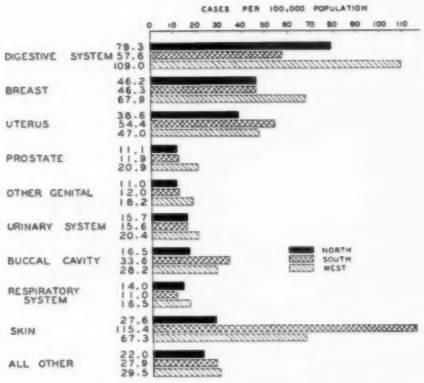


FIGURE 9.—Cancer cases of certain sites under treatment at some time during the survey year per 100,000 white population in surveyed cities of three geographic regions—12 large cities and surrounding counties, 1937–39. (Site refers to primary site. Cases refer to those residing within the surveyed area. Population estimates made from 1930 and preliminary results for 1940 census, assuming that the percentage of white persons was the same in the 2 years. See figure 10 for populations used.)

Considering both sexes combined (fig. 9), cancer of the buccal cavity, urinary

[6] *Death rates for all cities over 100,000 are derived as follows: North=simple mean of rates for Northeast and North Central cities; South=rate for southern cities; West=rate for Pacific cities. See Public Health Bulletin 257 (3) for the original data and details as to States included in each area. None of the rates as here used are adjusted for age differences; when the rates for all cities are adjusted to the population distribution of 1930 in the total United States they are: all, 133; North, 136; South, 116; West, 119.*

system, and skin all showed rates in the South that were equal to, or in excess of those in the North. The outstanding ones are skin, where the rate in the South was about four times that in the North, and buccal cavity, where the rate was twice that in the North. It will be recalled that these sites were also high for the South in the officially recorded mortality from cancer. The high incidence and low mortality in the South thus reflects the high proportion of all cancers that are skin cancers, which are not so important as a cause of mortality.

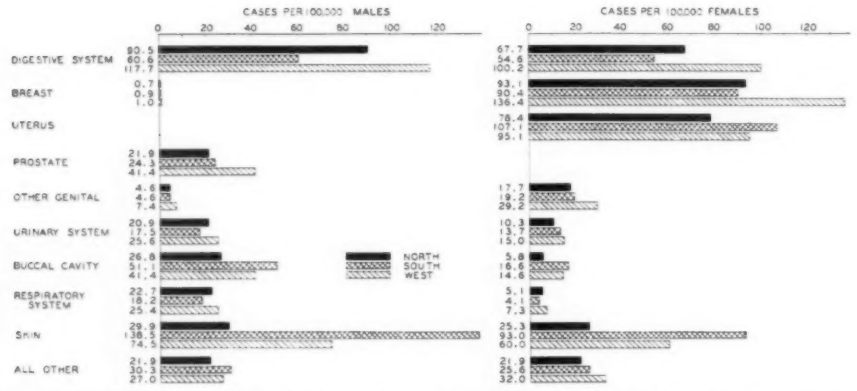


FIGURE 10.—Cancer cases of certain sites under treatment at some time during the survey year per 100,000 white males and females in surveyed cities of three geographic regions—12 large cities and surrounding counties, 1937–39. (Estimated populations: North, male, 4,384,700, female 4,258,508; South, male 742,163, female 764,462; West, male 700,052, female 684,819. Estimate assumes same sex ratios as in 1930. See figure 9 for other details.)

Site Distribution of Cancer

Among males cancer of the digestive tract constituted 38 percent of all cancer cases in the North, but only 18 percent in the South; the figure for the West was 33 percent. Among females cancer of the digestive tract constituted 21 percent of the cases in the North, but only 13 percent in the South. As in the official death statistics considered earlier, both breast and uterus are more important sites of cancer among females than is the digestive tract. Considering the other extreme, skin cancer among males in the North constituted only 13 percent of the total cases as compared with 40 percent in the South. Among females skin cancer constituted 8 percent of the total cases in the North and 22 percent of the total in the South—both figures being definitely lower for females than males, the ratio of South to North being roughly 3: 1 for each sex.

Specific Digestive Tract Sites of Cancer

If the eight different sites of digestive tract cancer are considered separately (fig. 11), the case rate in the South is low for both males and females for cancer of the stomach, intestine, rectum and anus, and esophagus. Among males, cancer of the liver, pancreas, duodenum, and other digestive sites all showed rates in the South that were equal to, or in excess of those in the North, but among females rates for cancer of the liver and duodenum were

lower in the South than in the North. However, some of these rates are unreliable because they are based on small numbers of cases.

digestive tract that are in each of the eight specific sites (fig. 12). According to this measure the South is, relative to other cancers of the digestive tract, somewhat low

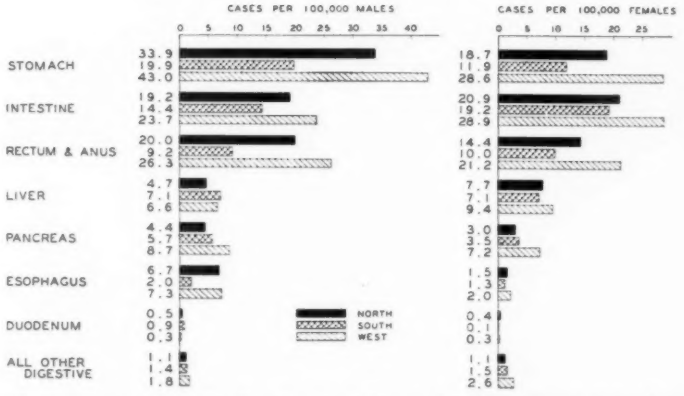
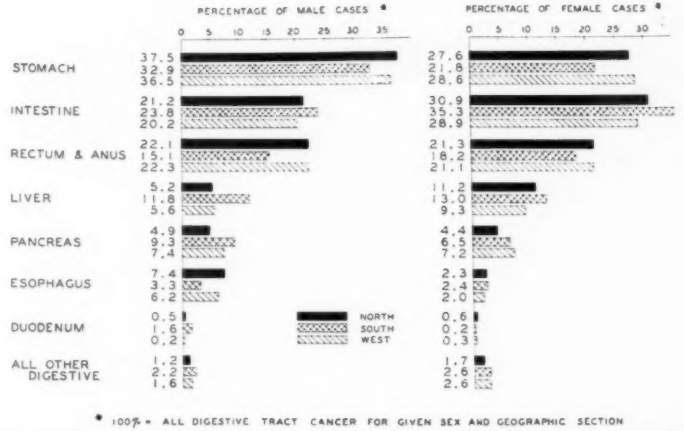


FIGURE 11.—Cancer cases of specific digestive-tract sites under treatment at some time during the survey year per 100,000 males and females in surveyed cities of three geographic sections—12 large cities and surrounding counties, 1937–39. (See figure 10 for populations.)

Another measure of the importance of the different digestive sites of cancer can be computed by taking for each geographic area the percentage of all cancers of the

in cancer of the stomach, rectum and anus, and, for males, esophagus; but cancer of the intestine, liver, and pancreas constitute higher percentages of cancer of



* 100% = ALL DIGESTIVE TRACT CANCER FOR GIVEN SEX AND GEOGRAPHIC SECTION

FIGURE 12.—Percentage distribution of digestive-tract cancer cases under treatment according to specific site, by sex and geographic region—12 large surveyed cities and surrounding counties, 1937–39. (Total cases digestive tract cancer: North, male 3,969, female 2,882; South, male 450, female 417; West, male 824, female 686.)

the digestive tract in the South than in the North. It must be remembered that the numbers of cases for some sites are small and the percentages therefore unreliable.

SUMMARY

Certain statistical studies of cancer with special reference to gastric cancer, undertaken by the United States Public Health Service, are summarized. The recorded mortality from all cancer has increased steadily since 1900. The cancer death rate among males has increased more rapidly than that among females; in 1935 the male rate was 87 percent of the female rate, as compared with 59 percent in 1900.

The trend of mortality from cancer of a given site differs for males and females, and for a given sex the trends for the various cancer sites differ. The recorded death rate from cancer of the stomach and liver among females increased from 1900 to about 1920, but decreased after that time. This decrease has affected chiefly persons under 65 years of age; among females above 75 years the death rate has definitely increased. Among males the recorded death rate from cancer of the stomach and liver increased until about 1922, but there has been a slight decrease since that time. This decrease has affected chiefly the age groups under 45 years; among males above 55 years the death rate has definitely increased.

The decreases since about 1922 in mortality from cancer of the stomach and liver among males and females occurred in each geographic region except the South, where there has been no decrease for males and only a slight decrease for females.

The highest recorded death rates from cancer of the stomach and duodenum in 1930–32 occurred in the Northern States from the Atlantic to the Pacific. In the Southern States the rates are uniformly low, Louisiana being the only one that does not fall among the 11 lowest States. The other sites of cancer of the digestive system also show high death rates in the North, although in some sites the Northwestern States are not so much above other sections, as is true of gastric cancer.

At the other extreme is skin cancer, for which all of the Southern States are among those with the highest mortality rates. Cancer of the buccal cavity (except lip and jaw) is likewise relatively high among females in all of the Southern States, but among males the North and South show no great contrast.

Surveys were made of cancers under treatment by physicians, clinics, and hospitals in 12 large cities. Among white persons in the northern surveyed cities there were 2.3 cancer cases under treatment during the year for each annual death, as compared with 4.0 in the South and 2.8 in the West. Considering all surveyed areas, there were 24 skin cancer cases under treatment for each annual death, but only 1.4 cases of cancer of the digestive tract per death.

Among white males in all surveyed areas 34 percent of the cancer cases were of the digestive system, as compared with 54 percent of the deaths. Among white females the corresponding figures were 20 percent for cases and 40 percent for deaths.

Considering all cancer, resident cases under treatment per 100,000 white population in the surveyed areas amounted to 282 in the North, 386 in the South, and 425 in the West. This showing is in contrast with death rates of 124 per 100,000 surveyed population in the North, 97 in the South, and 151 in the West. Thus the South shows a lower cancer death rate but a higher rate of cancer cases under treatment than in the North.

Cases of cancer of the digestive system under treatment in the white surveyed population of the North amounted to 79

per 100,000, as compared with 58 in the South, and 109 in the West. Cancer of the skin, on the other hand, amounted to only 28 per 100,000 in the North, as compared with 115 in the South, and 67 in the West. Prevalence rates of most of the other important sites of cancer were as great in the South as in the North.

Cancer prevalence rates per 100,000 white population were less in surveyed cities of the South than in those of the North for the three most important digestive sites—stomach, intestine, and rectum.

Acknowledgment is due to Mr. Arthur J. McDowell who was in immediate charge of much of the field work and tabulations for the prevalence studies.

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DISCUSSION

Chairman Smith: Dr. Little will open the discussion.

Dr. Little: Mr. Chairman, Ladies, and Gentlemen: I was fortunate enough to receive Dr. Collins' paper in advance, and I am sure that you will agree with me that he has covered in great detail and to our great advantage the phases of distribution of cancer related to geography and to sex in a way that requires no further comment. I have therefore assumed that because of the limited time and the broad scope of our program, it would be acceptable to all of us to try to introduce different methods of analysis and different points of approach.

I think that among his general points of emphasis, the one that is particularly important to many of us is the attempt which he has made, very successfully, to calculate the ratio of cases to deaths; because in this method which he is using, one gets a clue as to the success in diagnosis and the success in treatment in various sites in the body in various parts of the country—in other words, from the cancer-control point of view, which, after all, his data affect very basically. These studies

of relation of number of cases to deaths are extremely important, and I think that he has given us ample material so that at least the American Society for the Control of Cancer will be able to make some fairly important decisions as to where emphasis is needed on better diagnosis and on, perhaps, better treatment.

There is another method of tabulating data in connection with incidence of cancer which is available to those who will use the material given by the Bureau of the Census for the United States registration area. I shall take, if I may, a few minutes to show you this method, because it introduces the factor of competition within the body of different types of cancer at different ages in the life of the individual. Dr. Collins' very complete, useful analysis deals quite largely with extrinsic factors, the relation of environment, the relation of other factors to the incidence of cancer in the population as a whole. I should like to show you these charts in which the data are tabulated in a different way.

This method of tabulation is as follows. In the statistics available to us, the location of cancer according to sites is taken care of, as you know, in a routine manner; and the actual incidence is tabulated for each race, the white, the colored, and other races, and for each sex, in each age group, for different sites in the body. If you take, let us say, for white males all the cancer that occurs before 5 years of age and call that 100 percent, call that unity, you can then determine what proportion of that 100 percent occurs in the different sites in the body as indicated in these statistics. Then you do that for each age group separately, you do it for those up to 5 years, then from 5 to 9, from 10 to 14, from 15 to 19, as the data are divided; and having determined the proportion of cancer in each age group that occurs in each site, you can construct a picture of what is happening inside the body of the average white male person in the United States in relation to cancer risk at different ages.

I think perhaps if I hold up one of these charts you will see what I mean. Here is the youngest age group and here is the oldest recorded. In other words, you are moving from youngest to oldest in the population as you move in this direction, and here is the percentage of the total cancer in each of these age groups, one after the other, calculated separately, that occurs in different sites of the body. This is white males. Here is genitourinary, the commonest site of cancer up to 5 years of age. Follow this red line and you will see that as you study age groups these genitourinary tumors drop at first, then the line comes up again for testicular tumors, drops again, and comes up for the prostatic tumors in relation to other types of cancer at each successive age group. But if you look at the human individual quickly as he goes through life, you will see some very interesting things, that genitourinary tumor is the big risk up to 5 years. In the next age group it is the brain; in the next age group, the long bones; then long bones again; then testicular tumors; and then the digestive tumors take command of the situation as the greatest site of risk for men.

The advantage of this is that if one looks merely at the deaths per hundred thousand one says, "Well, testicular tumors are relatively rare," whereas the actual fact is that they are the greatest cancer risk for men 20 years of age. The adjustment of the urinary function apparently has something to do with early urinary tumors, possibly glandular; the brain is a great risk; the long bones fail to control

their growth as the individual approaches puberty; then come testicular tumors, and then digestive.

In the meanwhile, although the skin is relatively unimportant at first it moves up in position to the third most important site of tumor in very old age.

Looked at from the point of view of organs, the short time that the kidney, the brain, and the long bones are a risk is contrasted with the steady menace of the digestive function.

I think this gives one an interesting picture of the individual.

Here is the female chart. It is exactly the same as that for the males up to the time of puberty, or so near it that it is very striking. We find first the kidney situation, the brain next (only in the females it predominates in two periods and long bones in one, whereas it is the other way around in males), then breast and uterus become the commonest types of cancer in the early age groups from 25 to 30 on up to about 50, at which time digestive tumors take the lead. But if you take out the uterine tumors entirely and the breast, the digestive situation in both sexes is directly comparable.

Here is the male population with the prostatic and testicular tumors taken out, and the female population with the breast and uterus taken out, and the values recalculated on a new hundred-percent-base level. The solid line is the female risk of cancer of the digestive system, and the broken line the male. It is actually true that if you eliminate the reproductive-gland tumors the digestive system predominates the situation more in women than it does in men, which is a situation that you don't ordinarily pick up because the breast and uterus upset your statistics. If you get rid of the sex tumors, so to speak, the digestive system in women is a bigger risk as compared with other areas than is the case in men.

As Dr. Collins' figures show, in their statistics they divide stomach and duodenum into one group, intestines exclusive of rectum and anus into another, and rectum and anus into a third, and these are quite interesting when you compare just these areas. Here is the curve for the rectum in male and female, the female solid, the male broken; and there is practically the same risk running through—they are practically identical, they cross each other several times. In the stomach and duodenum, the male starts off differently, but once established the male is the greater risk. Exactly the opposite of this is true in the intestines other than the stomach and duodenum; and in the rectum and and anus, the female is the greater risk.

Here is the kind of thing, it seems to me, that we must try somehow to explain, because it is perfectly clear that the rectum and anus are not to be classed as the same sort of physiological risk in the sexes as are these other two sites, and there is something to be found out as to why there is this difference, with the men the stomach and duodenum being the major risk, and with the women the rest of the intestines.

The similarity of the sexes in regard to other sites is quite striking. Here, for instance, are the two brain curves, again the female solid, the male broken, showing no influence whatever of sex; the long bones are even more strikingly similar between the two; and here the genitourinary situation is simplified by showing first the male in this broken line with the testes and the prostate humps in the curve. Then by taking out cases involving the testes and the prostate so that the kidney and bladder only are studied, the male and female curves are practically

identical and go along here together. The excess of genitourinary tumors caused by the two glandular sites, the testes and the prostate, does not in any way reflect itself on any increased risk in the rest of the male genitourinary system, in the bladder and the kidneys.

I should like to point out that this type of tabulation may be very valuable not only in the statistical study of cancer, but also in the experimental, because while we are dealing with a mixed population in the case of these statistical data, it should be possible to show strain differences between inbred strains of animals by this same type of tabulation.

Chairman Smith: Dr. Macklin.

Dr. Macklin: Mr. Chairman, Ladies, and Gentlemen: I was very much interested in Dr. Collins' paper, and my one regret was that he did not draw some conclusions from his figures. He showed us geographic distributions of cancer, rising and falling death rates, the greater incidence of cancer cases as compared with cancer deaths in the South, etc., and I should like to have his interpretation of these differences. For example, we find from his charts that the death rate from all cancers among males is rising more rapidly than among females. I feel that this may well be due to the fact that males are peculiarly susceptible to lung cancer, and that in the period covered by the discussion, recognized lung cancer has increased in importance, having risen from the place in which it constituted about 1 percent of all cancers to that in which it forms from 10 to 20 percent of all cancers. This increase would affect the males particularly. We may therefore ask, Is it true that relatively more males are actually dying of cancer now than died before, or is it that the increased recognition of lung cancer among males raises the male cancer death rate unduly? Is it perhaps true that the male cancer death rate has not increased any more than the female rate from 1900 to 1935, and that the apparent excess of increase in the male rates is due merely to our more frequent recognition of lung cancer? This is one item which must be remembered when these total cancer death rates are interpreted.

Dr. Collins did point out one interesting interpretation of his charts, namely, that the high death rates from lung and pleural cancer in the Southwest are no doubt due to the migration of persons with tuberculosis, and other chronic respiratory diseases to the drier climate of the Southwest. They die there, and are found to have been suffering from lung cancer, not from tuberculosis, bronchiectasis, etc. The rates are for the most part not corrected for State residence, and so the Southwest appears to have the highest death rate from cancer of the lung. Here then is an explanation of the peculiar geographic distribution of lung cancer, which admits that these figures cannot always be accepted at face value.

I am wondering if there is not a similar explanation for others of the odd geographic distributions of different cancers found in these charts. With the exception of cancer of the mouth and pharynx, most of the cancer death rates here discussed were rather lower in the South than in the North. Does that actually mean that if you are living in the South, you are much less likely to have cancer of the stomach or the rectum than if you live in the North; or does it mean that you are much less likely to have your stomach cancer diagnosed in the South? When you consider the large Negro and poor white population of the South, who may get very inadequate, if any, medical attention in rural districts, who may die of a "misery" in the stomach which is in reality a gastric cancer, it would indicate that poor diagnosis, or none, probably explains the lower cancer death

rate in the South. Moreover, if the case rate incidence in comparison with the death rate is so much higher in the South than it is in the North, what happens to these excess cancer cases? Do they die of something other than their cancer, or do the persons who are financially able to do so migrate to the North to the larger medical centers for treatment, where some of them die and are listed in the northern death rates?

If you recall the charts shown this morning, and analyze them from the standpoint of accessibility of diagnosis, you will remember that when the cancer is inaccessible and hence hard to diagnose, such as cancer of the lung, stomach, prostate, etc., the cancer death rate is low in the South; but if it is obvious as are cancers of the skin, mouth and pharynx, or uterus, then the death rate rises in the South. Are these geographic distributions representative of fact, so that it is true that if an individual stays in the North he is likely to die of cancer of the stomach, whereas if he moves South he will not get that cancer, but will get one of the mouth or pharynx? Is it not more likely to be true that one will develop cancer of the stomach no matter where one lives, but one's chances of having it recognized and so entered into the cancer death statistics are greater in the North? It seems to me that this question of accuracy of diagnosis, based upon accessibility to adequate medical care, must be taken into account in the interpretation of all of these charts before we draw any conclusions that one area of the country has a high gastric cancer rate while another section has a very low one. If I accept these geographic distributions as indicating real differences in chances of developing cancer, I think that the choice I should make would be this: I should like to be a male, having cancer of the uterus, and living in the South.

Let us analyze the curves for stomach and liver cancer. We find in the charts that these two curves are flattening out in recent years; in other words, gastric and liver cancer appear to be increasing, but with the acceleration rate slower than that for all forms of cancer together. Is that true, or do we have to look below the surface to find other explanations? We also noted that the cancer death-rate curve for stomach and liver was flattening out more for women than for men. First, we must remember that primary cancer of the liver is relatively rare, and that most cancers of the liver are secondary. Next, we must recall that in the earlier years under discussion this morning, the secondary site of cancer was given as a cause of death in many cases; it has only been recently that insistence upon the primary site of the cancer being listed in the death certificate has altered this tendency. Therefore in recent years, fewer cancers of the liver are reported, because they are now reported as cancers of the prostate and uterus, for example. Since uterine cancer is frequent in the female and since the liver is a common site for secondary growths, the shift from secondary to primary site in reporting deaths from tumors causes a greater decrease in the case of the female than in the male. Therefore, the stomach and liver curves are flattening out in recent years, and more so in women than in men. Also, you will recall that the death rates from cancer of the intestine and peritoneum were rising rapidly while the curves for stomach and liver were falling slightly. Formerly, cancer of the intestines was put in with cancer of the stomach and liver; now that they have been separated, the death rates from cancer of the intestine naturally rise, while that for cancer of the stomach falls. Shift in diagnosis may apparently cause a profound shift in cancer death rates, whereas actually the same pro-

portion of men and women in any age group may be dying of the same type of cancer today that they died of 30 years ago.

I feel that we have to accept with caution some of the so-called extrinsic factors for cancer proposed by workers. Cramer, for example, cited by Professor Ewing in his fourth edition of Neoplastic Diseases, states that the poorer you are in the social scale, the more likely you are to get cancer of the stomach. I cannot help wondering if that is due to something quite different from one's social scale except quite indirectly. In England, if you are in the upper and middle classes you go to a private nursing home, but if you are unable to pay for private nursing homes you go to the charity hospitals where autopsies are done. Therefore many cancer patients among the upper classes might not be diagnosed as cancer, while a higher percentage of poor patients with gastric cancer would be so diagnosed. Also, one's chance to enter a hospital as a charity patient in England, depends, according to Simpson in his article on lung cancer, on the desirability of the patient as teaching material, since not all patients can be admitted, owing to lack of room. Therefore the more interesting case of two persons with about the same degree of illness will enter the hospital and become diagnosed. Perhaps these factors enter into the difference in incidence of gastric cancer in the different social classes in England.

Cramer also finds a definite relation between the condition of the teeth and the incidence of gastric cancer. That again may be due to the fact that the lower you are in the social scale the less money you have to look after your teeth, and also the more likely you are to enter hospitals where your cancer will be diagnosed.

What factors might cause gastric cancer in persons with poor teeth? I can think of two: One might be that persons with poor teeth might chew their food less thoroughly with the result that more work was thrown upon the stomach in the process of digestion. The other is that one might swallow purulent material from infected teeth, and cancer might be thought to develop in the stomach through chronic inflammatory changes. But such persons who would come in this category in the South apparently are not getting gastric cancer, for the rates in the South are low, and yet the per capita wealth in the South is not high. Also persons with chronic respiratory disease, who cough up and sometimes swallow purulent material from the lungs, do not have a high incidence of gastric cancer. Just what is the relationship between poor teeth and gastric cancer I do not know. It does seem that we find two or three things associated and jump to the conclusion that they are causally related, whereas there may be no relationship whatever.

I should like to make this suggestion. Coming as I do from a country which is at war, and which has no money to spend on these things, i have to make this suggestion to you in the United States, which is the last large country left where you can turn your attention to factors not immediately related to war. In the collection of data for death statistics, would it not be a good idea if we included on the death certificate not only the disease assigned as a cause of death, and one or two main contributing diseases, but also every disease from which the person suffered at that time? For example, a woman has a cancer of the uterus but she also has a cerebral hemorrhage. She cannot die of both, and since neither one can be regarded as a contributory case of death when she dies of the other of these two diseases, only one of them is entered on the death certificate. If she dies of her cerebral attack, that is the cause of

death; but had it not come then, she would have died of her advanced cancer of the uterus within 2 months and would have been listed as a cancer death. A woman has had cancer of the rectum, has been operated upon, and has no recurrence locally; but 5 years later she develops recognizable metastases in the lung. Is she entered as a lung-cancer death, or as a rectal-cancer death? If you put in primary site, she is a case of death from rectal cancer, but if you put in what really killed her you put in cancer of the lung. But while she is dying of her lung tumor, she has a cerebral hemorrhage which is fatal in a few hours. What is her category, cerebral hemorrhage from which she died, or cancer from which she was about to die in a few days? I cite these two as actual cases.

In the collection of death records we should have all of the diseases from which the person suffered at the time of death. A man who has diabetes and is killed in an accident should not be listed merely as an accidental death but as a sufferer from diabetes. Since we can only die of one cause, it is evident that the cancer death rate is dependent not only upon the number of persons who die of cancer but also upon the number of other diseases which may kill persons with cancer before the cancer kills them. The interpretation of the incidence of cancer of any organ depends, therefore, upon our correct interpretation of all other factors influencing the death rate of persons within the cancer age.

I would make this second suggestion: It may be a Utopian dream, which may be realized in the future, even if not now. We should approach the matter of gastric cancer as well as other forms of cancer from a new angle. Instead of analyzing only a population who has already had gastric cancer, we should study a population which, as far as we know, has as yet no gastric cancer. We could study them carefully, tabulate their physical findings, study them for the onset or the presence of the five main types of cancer, let us say, cancer of the lung, stomach, and rectum, and in the female, cancer of the breast and uterus too. We should have a complete record of dietary habits, of chronic respiratory diseases, of the amount of alcohol they consumed, of how much they smoked, of how many children the women bore, and whether or not they nursed them, etc. Then when they died we would have an autopsy and record all the pathological findings. The persons with gastric cancer could then be studied with respect to any one factor which might have been a cause of gastric cancer, and could be compared with a control group of the same age and sex distribution that did not develop gastric cancer. Where would you get such a population? I would suggest that the government employees be the experimental population. You might make it a condition of employment that they enter into this scheme. It would be of distinct advantage to them for they would receive all their yearly or semiyearly examinations free, from experts particularly interested in special fields. Their climatic conditions would be more or less controlled, for all of them would be living in Washington; and all would be subjected to the same expertness of diagnosis. From such a study, you might derive much valuable information which cannot be obtained from a study of a population which has died of gastric cancer.

Finally, I should like to ask Dr. Collins to give us an interpretation of some of these figures. I should like to ask him if he thinks that if you live in the North you are more likely to develop cancer of the stomach than if you live in the South, and if so, what factors induce stomach cancer in the North and inhibit it in the South. Or is it that you will have gastric cancer

no matter where you live, but that you are more likely to have it diagnosed if you live in the North, than if you live in the South?

Chairman Smith: We shall now have a general discussion on this topic.

Dr. Alvarez: I know we are all very grateful to Dr. Collins for this most interesting study, and I am sure that we do not have to remind him of the things that he would like to have picked up in the way of further information.

In view of what Dr. Macklin said about the dangers of statistics, I am reminded of a survey once made by the Scientific American to find out if it is true that people tend to die more often at a certain time at night. As I remember, the data were taken from some big city hospitals and showed that the great peak of death comes about a quarter of seven in the morning. To me, this was amusing, because years ago, when I was working in a big hospital, we interns got around the night nurses and arranged that they would not take official notice of the death of a patient until morning. They would pull the sheet up over the head and not call us to certify death until a quarter of seven, when they went off duty, so we wouldn't have our sleep disturbed. That probably was the origin of that tremendous peak at a quarter of seven. This is a beautiful example of how statistics can deceive if we do not know all the facts.

I did not hear Dr. Collins say if his figures were corrected for age. It seems to me that this has to be done in all cancer work, because, for example, southern California is now a refuge for old people, and therefore a high incidence of cancer should be found there. Then, there is a need for correction for the presence of large medical centers. I wonder if it was possible in these studies to, in a way, put the people back into the State from which they came. Because of the presence of the Mayo Clinic in Minnesota, one should find recorded there a huge death rate from rare diseases, such as Hodgkin's disease. I notice that Louisiana stood out as having an unusually high death rate from carcinoma, and I wonder how much the Touro Infirmary and some of the other medical centers in New Orleans have to do with that. Doubtless many persons from other parts of the South go to New Orleans when very ill, and some die there.

We all wonder how much better powers of diagnosis have to do with the increase in reported cancer death rates. For instance, I saw recently a man who, to all appearances, died of stroke. But when we autopsied him, we found he had died of a cerebral metastasis from a lung carcinoma so small that we could hardly have demonstrated its existence during life even if we had looked for it.

It is notorious that rectal carcinoma is poorly diagnosed. I think four out of five of the cases of rectal carcinoma that we see at the Mayo Clinic have been diagnosed elsewhere as cases of colitis, or diarrhea, or bleeding hemorrhoids.

Some day someone must make a big study like this on information obtained only from necropsies, and well-done necropsies made preferably in emergency hospitals and morgues where many persons die sudden deaths from accident or acute illness. Necropsies at a place like the Mayo Clinic cannot be used statistically very well because most of the patients come to Rochester because they are sick; most of them are seriously ill, and when they come to us many know that they have carcinoma. Hence, I don't know how we could use our statistics to show much about the incidence of the disease in this country.

As I remember, at the Clinic, the incidence of carcinoma of the colon has been going up remarkably. But it might be going up simply because our surgeons are

operating successfully on many patients with this disease. Others with it hear about this work and they come for help. Who knows?

I think we ought to begin soon to gather statistics to show whether the increase in the amount of smoking done by women is increasing the incidence in them of carcinoma of the upper part of the respiratory and digestive tracts.

Dr. Tannenbaum: The statistics in Dr. Collins' paper on the morbidity and mortality of cancer are dependent on the additive effects of all of the factors that determine the incidence and diagnosis of cancer. I should like to comment, briefly, about our investigations on the effect of one factor, nutritional restriction, on the incidence of cancer.

In work on this problem done in our laboratory, pure-strain mice and various types of tumors were utilized—spontaneous tumors of the breast and lung, and epitheliomas and sarcomas induced by the carcinogenic hydrocarbon, benzpyrene. The control full-fed mice were fed an adequate basic diet, while the experimental weight-restricted mice were fed the indentical diet but in amounts ranging from one-third to one-half that fed the control animals. In the underfed groups, tumors developed in markedly fewer mice and at a later time than in the corresponding control group. The mice of the weight-restricted groups appeared healthy and lived longer than did the mice of the control groups. These results were obtained with all strains of mice and all types of tumors studied.

In order that we might ascertain whether or not the same relationship holds for human cancer, data available from a number of insurance studies were evaluated. Analysis of eight insurance studies revealed, with one exception, that the tendency to develop cancer is greater among individuals who are overweight than among those of average weight or less. Thus, in both animal and man, it appears that individuals of average weight or less are not so likely to develop cancer as are those who are overweight.

Unfortunately, the studies along these lines with regard to tumors of particular sites, such as gastric carcinoma, are few in number. Hunter studied more than 1,000 deaths from cancers of the "digestive tract or peritoneum," comparing the weights of the individuals at the time that they obtained insurance policies with those of a suitable control group. The average weight of those who later developed cancer was 2.3 percent higher for males and 5.4 percent higher for females than the average weights of the respective controls. Dublin, in studies on causes of death in women, also gives data on cancer of the stomach. A critical examination of these figures reveals no distinct relationship between weight and cancer incidence. However, only about 200 cases were studied. Obviously, more extensive investigations are necessary.

It seems that both the animal studies and, on the whole, the insurance statistics suggest that moderate nutritional restriction may have a significantly preventive effect on the development of cancer.

Dr. Cowdry: Mr. Chairman, I was much interested in this discussion, and like others I have been asking myself the why and the wherefore of these differences.

It seems to me that reasons demanding research at the cellular level, and thus nearer to the actual malignant change, are even more impelling than those involving the body, or even an organ, as the unit. Cancer is a cellular problem. It is known that some types of cells are more likely to become cancerous than others, and it is possible that certain of them never undergo this transformation.

Data should, in my opinion, be collected on the incidence of the malignant change in each of the principal types of cells of the human body. Our knowledge as to the structure and function of some of the types is fairly comprehensive, and our information about their intimate tissue fluid environments is slowly increasing. They are not of uniform properties for each is adjusted to the needs of its cellular constituents.

If a convincing case can be presented for the collection of data on the incidence of the malignant change in different cell types, the next question is the feasibility of such a project. The first step would be to ascertain what information on the subject is available and whether it is suitable for statistical analysis. While this is being done, a decision could be reached on the cell types to be included in the study. It would, of course, include those capable of multiplication and exclude old, highly differentiated cells like neutrophilic leucocytes and many others.

Since relative incidence can only be based on complete examination of all cell types under investigation, the survey would have to be limited to autopsies. It would be essential to achieve uniformity in the search at autopsies for primary sites of malignant change and to identify the cell types exhibiting it by histological examination. Standardized clinical histories of all cases would also be required.

The primary goal might be set at 10,000 autopsies of males in the decade of highest general cancer incidence and as far as possible in population areas similar geographically and in other respects.

Obviously the United States Public Health Service alone would be capable of organizing such a survey of the cell-type incidence of cancer. When the cell types studied have been arranged in order of increasing incidence, the best available advice might be sought from chemists, physiologists, and pathologists in a concerted effort to relate high and low incidence with cellular structures, function, and tissue fluid environment.

There is reason to think that in a given individual the hereditary endowment of all somatic cells is the same. Differential incidence of malignancy would appear to depend either on the special properties acquired in growth and differentiation, which may condition susceptibility to malignancy, or on differences in exposure to some factor promoting malignancy, or on both.

Because the malignant transformation can be brought about by ultraviolet light or by a variety of chemicals and is prone to occur in atrophic gastritis and in regions of chronic irritation, does not necessarily indicate that there are many fundamental causative factors. It is possible that all of these influences when brought directly to bear upon the cells may deliver the same kick or punch which permanently alters them and their descendants. When, therefore, the data are assembled for analysis, if indeed it seems to you worthwhile to collect them, one of the tasks for us to attempt, backed by our present slight knowledge of cellular physiology, is to discover a common denominator.

Dr. O'Brien: In the literature to date, squamous-cell carcinoma of the anus has been reported more prevalent in the female than in the male. Of the 1,424 rectal malignancies admitted to the New York State Institute for the Study of Malignant Diseases, 70 were squamous-cell carcinoma of the anus which represented 4.9 percent of the total rectal malignancies. This number treated and observed is fairly large, and I believe conclusive deductions can be drawn as to their distribution between sexes. I found the incidence of squamous-cell cancer of the anus in the

male and the female to be about equal.

Chairman Smith: I will ask Dr. Collins to close.

Dr. Collins: I certainly cannot answer all of the questions which have been brought up, but I can answer a few of them.

I am thoroughly sympathetic with the idea that we must look back of these statistics to get their true meaning. I had no idea of presenting them as incontrovertible facts.

As to correction for age, all of the mortality rates which I showed for all ages were corrected for differences in age distribution.

As to correction for residence, the rates were not corrected for residence. I showed no rates by size of city because correction for residence by size of city is a very large item; that is, the large cities with hospital facilities draw in many cases from outside the city and consequently many nonresidents die within the city. Correction for residence for States is not as important as it is for cities. For one year, 1935, the United States Bureau of the Census tabulated cancer deaths by residence of the patient, and when State rates are corrected for residence the corrections are generally fairly small. There are a few rural States (Idaho, Nevada, Wyoming, and North Dakota) in which the correction for residence increased the rate for that year by 10 percent or more, but for the great majority of the States the correction is less than 5 percent. In data not corrected for residence, Minnesota, Maryland, and Louisiana stand out with rather high rates because of greater hospital facilities, but for this 1 year in which residence-corrected rates are available, the general appearance of the map for all cancer does not change materially.

For the same year, 1935, data are available for residence-corrected rates by size of city. In every one of the six geographic areas that were examined, the residence-corrected cancer death rates were considerably higher in large cities than in small cities or in rural areas.

The difficulty of diagnosis of cancer of a given site is undoubtedly important in statistical comparisons. There is one definite exception to the general rule that the more easily diagnosed cancers of external sites are higher in the South—breast cancer is low in the South and high in the North.

One other point might be noted on the question of geographic variation and cancer diagnosis. There seems to be no reason why the cancer-prevalence studies should show a higher prevalence of cancer in the South than in the North if all the geographic difference is due to variation in the recognition of cancer. Yet you will remember that the South showed a higher prevalence of all cancer than the North. If the low cancer death rate in the South is all due to under-diagnosis, it would mean that the cancer prevalence rate would be extremely high in the South when account was taken of unrecognized cancer.

Regarding the question of diseases other than the primary cause of death, the United States Bureau of the Census, which is the official tabulator of mortality statistics, is beginning now to tabulate routinely the contributory causes of death. The Bureau plans to tabulate two contributory causes and publish some data for each year. Heretofore, there were only 2 years in which contributory causes had been published, 1917 and 1925. Only two contributory causes will be considered, because a trial tabulation of death certificates indicated that three causes covered most of the items entered on death certificates.

A living study in which a group of people would be followed throughout life would be ideal. However, cancer is relatively

rare, and such a large number of people must be followed through to obtain statistically significant cancer rates that such a project is a very large undertaking.

Chairman Smith: The next paper is Early Diagnosis of Cancer of the Stomach; Gastroscopy and Gastric Biopsies, Gastrophotography, and X-Rays, by Dr. Rudolf Schindler, Associate Professor of Medicine, University of Chicago.

Early Diagnosis of Cancer of the Stomach; Gastroscopy and Gastric Biopsies, Gastrophotography, and X-Rays

By Rudolf Schindler, *associate professor of medicine, Department of Medicine, University of Chicago*

Will you permit me to start with a rather personal remark. First, I am unable to tackle the problem of how to fight gastric carcinoma and how to diagnose it at an early stage, purely from the viewpoint of the specialist. I believe that we can evaluate special techniques only if we consider the possibility of applying them practically in average conditions and of joining them with the general clinical aspect. Secondly, I want you to understand that the suggestions I shall try to make have not been derived from a purely scientific and research viewpoint. In gastric cancer more than in any other cancer we have to consider the psychological situation; no fight against this disease is possible without the realization that we are dealing with one of the most frequent causes of death; and we have to realize that the general attitude of the layman and of the physician, also, and even of the specialist in gastroenterology is not an optimistic one. The aspect of treatment of gastric cancer is on the whole a very gloomy one (*1*); and whatever results we may obtain with a special method, we have to ask ourselves whether or not this special method will take away some of that gloom. If a disease is a deadly one, then its better recognition will not help us to come to a fight against it. And if, as I shall show you, the development of X-ray and gastroscopy has led to an almost infallible diagnosis of gastric cancer, then such a statement does not mean that this will help us to improve the results of treatment of gastric cancer.

The statistical data about cure in gastric cancer under the present conditions are known to you. They are summarized in the table (fig. 1) taken from Livingston and Pack (*2*). In the long column at the left you see all cases admitted to a clinic or a hospital because of gastric carcinoma, and at the right the three small columns represent cures of 3-years, 5-years, and 10-years duration. Five-year cures are obtained on the average in only 1.9 percent, the highest reported average being 5.1 percent. And if we consider, not the conditions of some outstanding clinics or hospitals, but the conditions under which the general practitioner and even the urban physician has to work in this vast country, then we cannot expect to obtain better than average results. Livingston and Pack do not believe that the results of treatment of gastric carcinoma as demonstrated here can be improved with our present methods. Thus, on the average not more than 2 percent of all gastric carcinoma cases which enter a clinic or hospital can be cured; 98 of 100 cases will die in spite of treatment, and this is a result which necessarily must affect psychologically the attitude of public opinion, and in the long run, in spite of all propaganda, the attitude of the practitioner also. In scientific meetings we have every right to point to the wonderful results of gastric resection which permits a definite cure in 20 percent of all

cases in which a resection is possible (*3*). But for a program of national health service these cases, although so very gratifying in themselves, unfortunately

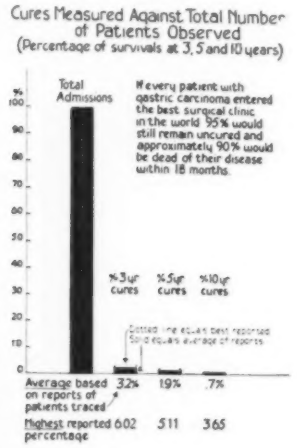


FIGURE 1.—Surgical cures in gastric carcinoma. (Table from Livingston and Pack, End-Results in the Treatment of Gastric Cancer, p. 113. Reproduced by courtesy of Paul B. Hoeber, Inc. New York.)

disappear in the multitude of failures. In considering any single case, we have the right to be optimistic, and we have to go ahead with surgery; we cannot refuse any patient the chance of his being one of these 2 percent. But in a general program we have to realize that failure to cure more than 2 percent means defeat in a fight against a common disease.

GASTROSCOPY AND GASTRIC BIOPSIES, GASTROPHOTOGRAPHY AND X-RAY

I have been invited here to discuss the aspects of gastroscopy and gastric biopsies, of gastrophotography and of X-ray examination. I want to discuss first what these methods can do now for the recognition of gastric carcinoma, and second I want to demonstrate how these methods can be used in order to find new ways of approach to a systematic and general fight against gastric carcinoma.

GASTROPHOTOGRAPHY

First, let me dismiss gastrophotography with a few words. Photographing the interior of the stomach can be done in two different ways. The first method is that of the gastrophotor (*4*, *5*). A small photographic camera is introduced at the end of a thin tube into the interior of the stomach, and small films are exposed through pin holes. I have tried out this method myself over a long period of time. The results obtained in this way are entirely unsatisfactory. The pictures are full of artifacts. No orientation within the large cavity of the stomach is possible. These devices, although ingenious, must be considered mere toys.

The second method is photographing through a gastroscope. This has been done by Elsner (*6*), Henning (*7*), and by myself (*8*) by photographing through the rigid gastroscope. The technique used is that of a mirror reflex camera. The observer sees and takes the picture at the moment in which the lesion is in the center of the visual field. The results were rather nice as far as the relief was concerned, but unsatisfactory concerning the colors and the detail (fig. 2). Figure 2 is a photograph of the angulus of the stomach, and figure 3 is a picture of the normal folds of the gastric mucosa. Figure 4 is a photograph of a carcinoma of the stomach; and although the tumor is seen very well, the finer detail of its surface and the relation to its surroundings, so important for practical decisions, do not come out very clearly. I believe that we shall develop photography through the safe flexible gastroscope also; but gastrophotography will remain a method of recording, not a

method of diagnosis. The first attempts have been made.

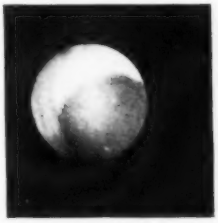


FIGURE 2.—Gastrophotograph of the angulus made through the Schindler rigid gastroscope. In the right and lower half of the picture the greater curvature of the antrum is seen; the lesser curvature appears in the left upper half.

FIGURE 3.—Gastrophotograph (made through Schindler rigid gastroscope) of normal folds of the posterior wall. Note the many bifurcating and cross folds.

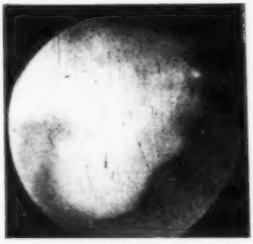


FIGURE 4.—Gastrophotograph (made through Schindler rigid gastroscope) of a polypoid gastric carcinoma. The tumor is well demonstrated, but the finer detail of its surface so readily seen in the gastroscopic picture does not come out in the photographic picture.

GASTROSCOPIC AND X-RAY EXAMINATION

X-ray examination is the chief method for the recognition of gastric carcinoma. With this statement I certainly do not intend to minimize the importance of gastroscopy. Most carcinomas can be seen with both methods. Some are not seen by gastroscopy either because gastroscopy is not possible, as in cases of cardiac obstruction by the tumor, or in cases of leather-bottle stomach in which the stomach cannot be distended by air and therefore no picture can be obtained, or because in a few cases the carcinoma may really be hidden, lying in one of the so-called blind spots of the stomach. On the other hand, some carcinomas may not be found by X-ray at the first examination.

In our material there was only one case in which both methods failed to reveal a gastric carcinoma. And I believe that if we should have to reexamine this case we probably now should make the diagnosis with both methods. At X-ray examination some kind of lesion was suspected at the lesser curvature; at gastroscopy an area of circumscribed, bleeding, hypertrophic gastritis of the posterior wall of the antrum was diagnosed. Thus, pathology was found by both methods, only the interpretation was not correct.

Dr. Frederic Templeton, our roentgenologic collaborator, to whom I owe almost all roentgenological data and almost all X-ray slides, and I agree that close cooperation between the X-ray examination and gastroscopy will bring about the best diagnostic results concerning gastric carcinoma. X-ray examination, however, is widely known, while gastroscopy is in the beginning of its development (*9–14*). But I hope that in a few years the valuable, close cooperation between the two methods will be feasible in all larger communities of this country. X-ray examination, however, will have such good results only if the routine, complete filling of the stomach is used, and if also the modern method of relief technique with compression and with the use of spot machines is employed.

This method consists of filling the stomach with a very thin layer of barium, by compressing the various portions of the stomach and by taking so-called spot films

FIGURE 5.—X-ray picture of a gastric carcinoma. Complete filling. Only a small defect is seen.

of regions which look suspicious. Since about 1928 the superiority of this technique has been obvious. I believe that we should insist on considering this method as indispensable for the recognition of early lesions and for the demonstration of the extent of a lesion. In figure 5 a small filling defect is seen with complete filling. On the relief film, however, the entire tumor is outlined (fig. 6). Only by means of the relief method was the tumor shown in figure 7 visible. I have to admit that in rare cases the relief method leads to the wrong positive diagnosis of a small gastric carcinoma, which, however, may then be corrected by gastroscopic observation. I believe that everybody would diagnose a carcinoma from figure 8—an apparent crater surrounded by a wall. But at gastroscopic examination a rather mild, polypoid antrum gastritis was seen. The patient is still living after 21 months, and the gastroscopic examination now reveals a perfectly normal antrum. However, such an occasional error cannot diminish the value of the relief method, just as a wrong gastroscopic diagnosis cannot diminish the value of the gastroscopic examination, if it is carried out by a well-trained observer. However, emphasis has to be laid on the words "well trained." Too many people possess X-ray apparatus who are not qualified to make careful X-ray studies; and I am equally afraid that people will buy gastroscopes now without realizing that a thorough training in interpretation is necessary in order to prevent these methods from being discredited. Training of highly qualified roentgenologists and gastroscopists certainly must be an important point in our program against carcinoma.

It is obvious from our experience mentioned above that almost no case of gastric carcinoma will be overlooked if the X-ray relief method and gastroscopy are used. The extent of the tumor usually can be well demonstrated by the use of either one or the other method (fig. 9). The niche

FIGURE 6.—Same case as figure 5 (relief technique). The entire tumor is outlined.

of a carcinoma is seen on figure 9, but whether or not the cardia is involved cannot be seen. However, at gastroscopy (fig.

10), the necrotic tumor was seen to go right up to the cardia. On the other hand, gastroscopy may be unable to reveal a carcinoma of the cardia, and then X-ray may be able to prove the extent of the involvement of the cardia. Some courageous surgeons (*15*) [1] now dare to cut through the esophagus in order to remove cardiac tumors, but even they want to be informed in advance as to whether they will find the cardia involved or whether a resection can be made through the gastric wall.

In spite of these gratifying developments in the field of early diagnosis, the differential diagnosis, in some cases, between gastric carcinoma and other diseases may be very difficult even when both methods are employed. The difficulty in differentiating benign and malignant ulcer is well-known. Now here is a point in which gastroscopy is superior to X-ray examination. And therefore it should be known that gastroscopy, if carried out after adequate training, is technically an easy and a safe procedure (*16*). Among 22,351 gastroscopies only 1 fatality has been reported (*17*), which probably was not caused by

FIGURE 7.—X-ray picture of a carcinoma of the fornix, visible only with application of relief technique. White arrow indicates tumor.

[1] *The patient, according to a personal communication of Dr. Dallas B. Phemister, is still alive and well 3 years after the operation.*

gastroscopy but by a preceding bronchoscopy. To the patient, gastroscopy is a minor office procedure, in full contrast to open-tube procedures like esophagos-

FIGURE 8.—Apparent filling defect with apparent central ulcer crater found at X-ray compression relief technique.

copy and bronchoscopy. No real discomfort will be felt after a good anesthetizing of the throat. After the inspection of the stomach, which lasts 2 to 5 minutes, the patient can leave for work immediately. Many of our patients in Chicago are examined at regular intervals in order to follow the course of their disease, and some have been examined more than 40 times. The fact that gastroscopy causes so little discomfort will play a great role in my suggestions in the last part of my presentation. Concerning the differential diagnosis between benign and malignant ulcer, gastroscopy, as I said before, is the superior method, but it is by no means infallible.

I believe that on four occasions I have made the diagnosis of a carcinomatous ulcer when later the course demonstrated that a benign ulcer had been present. But these cases are rare exceptions. Usually at X-ray the difficulties of this differential diagnosis are great, but at gastroscopy one glance is sufficient to decide the question. This is a statement which is never believed

by surgeons and pathologists. They know—I naturally know, also—that in the gross specimen such a differential diagnosis may be entirely impossible. How then should the gastroscopist be able to make such statements? It is too easily forgotten that in our beautifully sharp and colorful gastroscopic pictures we see living tissue, that the blood is circulating, that the color is not the dull, grayish-pink of the gross specimen after surgery or autopsy, but that there are striking contrasts between the orange-red, brilliant, glistening, normal mucosa, and the yellow, or gray, or yellow-gray, or white, or dirty-brown floor of an ulcerated surface. Figure 11 is the typical gastroscopic picture of a benign ulcer. It is characterized by its entirely sharp, punched-out edge. When, however, the ulcer pictured in plate 1, *D*, was observed, not even the idea of a benign ulcer

FIGURE 9.—X-ray picture of a carcinomatous ulcer of the lesser curvature. This picture does not indicate whether or not the cardia is involved.

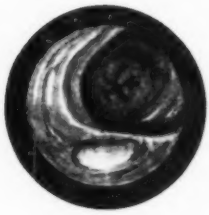


FIGURE 11.—Gastroscopic picture of a benign ulcer. In the background the closing pylorus is seen. The curve of the angulus separates the antrum of the stomach from the body of the stomach. A benign ulcer is seen to lie in the mucosa of the lesser curvature. It is elliptical and sharply punched-out. Its brilliant whitish floor contrasts with the surrounding orange-red mucosa. No inflammation is visible.

FIGURE 10.—Same case as shown in figure 9. Gastroscopic picture. The necrotic tumor is seen to involve the cardia.

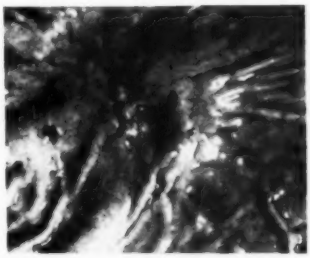
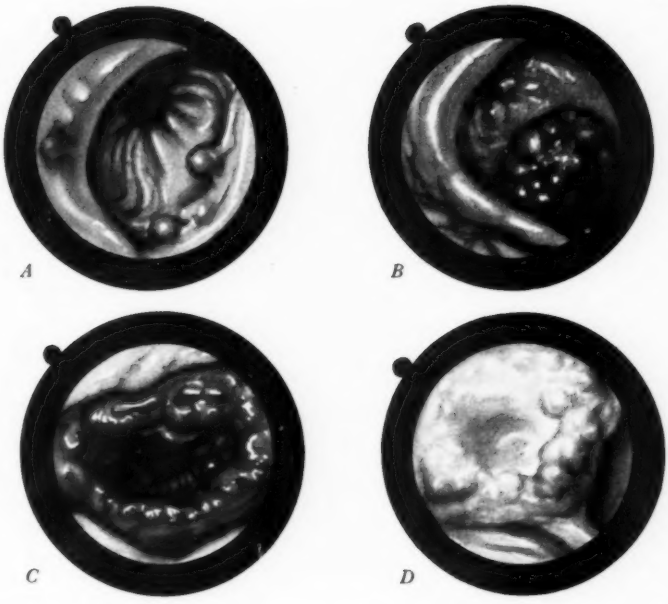


FIGURE 12.—Photograph of gross specimen of the carcinomatous ulcer, the gastroscopic picture of which is shown on plate 1, *D*. In contrast to the gastroscopic picture, the edge of the ulcer appears here sharp and punched-out.



A, Gastroscopic view of four adenomatous polyps. The gastric mucosa in which the polyps originated is entirely normal, being smooth and orange red in color. (In many other cases adenomatous polyps develop in atrophic gastric mucosa.) The parabolic curve (seen between 2 and 6 o'clock) is the so-called angulus. At the right the antrum is seen. In its background the dark, round hole of the pylorus is visible. Three of the polyps are located in the greater curvature of the antrum. The fourth is in the lesser curvature above the angulus. *B*, Gastroscopic picture of a type I gastric carcinoma originating on the soil of atrophic gastritis. Region of the stomach is the same as in *A*, but the gastric mucosa looks greenish gray; above the angulus in the anterior wall, purplish-blue blood vessels of the submucosa are visible, because of the thinning of the mucosa. A hemorrhagic, dark-red polypoid tumor mass is seen in the greater curvature of the antrum. *C*, Gastroscopic picture of a type II gastric carcinoma. A large ulcer is seen in the center, the floor of which is dirty in color. It is surrounded by a high, dark-red, nodular wall. Shallow ulcerations are seen in its upper circumference. The wall is sharply defined toward the surrounding, very pale mucosa. *D*, Gastroscopic picture of a small area of carcinomatous infiltration immediately above the angulus in the lesser curvature. The mucosa is stiff and somewhat nodular. In the center is seen a dirty-gray ulcer, the edge of which is blending with the surrounding mucosa and which has not the sharp, punched-out appearance of the benign ulcer (fig. 11). This is a type IV gastric carcinoma.

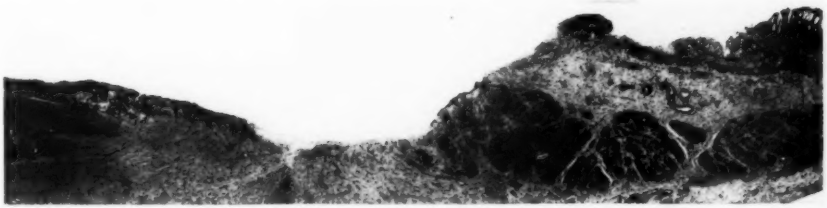


FIGURE 13.—Same case as figure 12 and plate 1, *D*. Microscopic section through the ulcer showing a mucosal carcinoma partly digested away by the acid gastric juice and thereby giving the gastroscopic impression of an unsharp edge.

came into our minds. The blending edge proved definitely the malignant nature of this ulcer. When the patient died and an autopsy was performed, the pathologist also diagnosed at first a benign ulcer, because he saw, in contrast to the gastroscopist, a sharp and punched-out margin (fig. 12). But the microscopic examination (fig. 13) revealed the carcinoma. Figure 13 reveals that the superficial carcinoma has been partly digested away, and that thin layers of carcinomatous cells and small islands of carcinoma are growing within the ulcer floor. This was not seen in the bloodless specimen, but this irregular blending was readily seen at the gastroscopic examination. To make this point still clearer, let us take a section of a benign ulcer and of a carcinomatous ulcer (fig. 14). Both would look exactly alike in the gross specimen. The depression would be seen to form the ulcer floor, but the carcinomatous infiltration invades the ulcer floor and gradually undermines the gastric mucosa, and this gradual blending can be seen at the gastroscopic examination. Therefore, I think that patients in the carcinoma age (older than 35 years), in whom an ulcer niche is found at X-ray, should be examined gastroscopically. It probably is no longer necessary to point out that the size of the ulcer does not mean anything. Tremendously large niches may be entirely benign, and very small lesions may be malignant. But it probably is necessary to point out that the therapeutic test alone, the watching of the roentgenologic niche becoming smaller, is not sufficient evidence that the ulcer is benign. Figure 15 contains a sequence of pictures of a patient in whom a niche disappeared gradually. But at the very first gastroscopic examination undertaken at a time when the X-ray niche was still large, an infiltra-

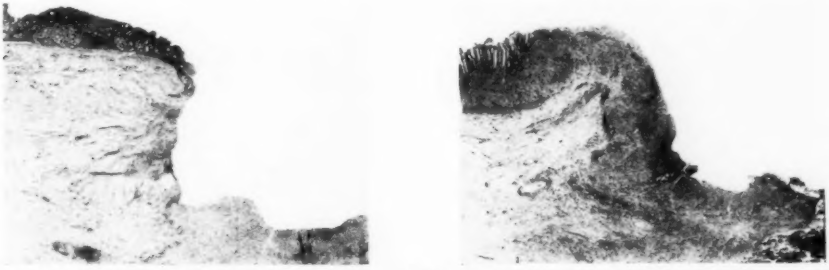


FIGURE 14, *A* and *B*.—Microscopic sections through the edge of *A*, a benign ulcer; and *B*, a carcinomatous ulcer. In the gastroscopic picture the gradual carcinomatous infiltration of the mucosa can be seen because of the circulating blood.

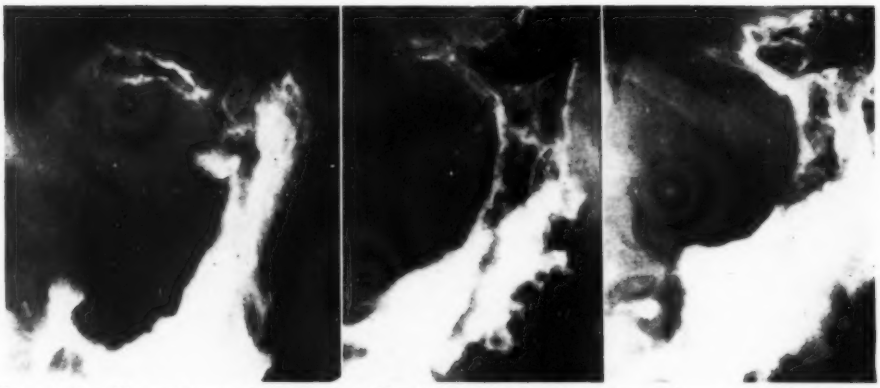


FIGURE 15.—X-ray picture of a diffusely infiltrative type of gastric carcinoma shown gastroscopically in figure 24, and confirmed by autopsy. In the beginning a deep niche was seen which suggested a benign ulcer at the time at which gastroscopically carcinoma was diagnosed with certainty. This niche is seen to disappear gradually.

tive carcinoma involving the entire stomach was seen, and this carcinoma was found 2 years later at autopsy. Therefore, I believe that gastroscopy should supplant the therapeutic test whenever possible.

As said before, gastroscopy is not infallible, and it cannot be infallible. In his paper on benign and malignant gastric ulcers, Palmer (*18*) came to the following conclusions:

(1) The existence of a carcinomatous degeneration in benign ulcer remains to be proved conclusively.

(2) Peptic ulceration of carcinoma may produce a lesion grossly indistinguishable from benign ulcer.

(3) Although there is no pathognomonic sign to indicate the benign nature of a lesion, the total evidence available from careful study permits the clinical differentiation of benign and malignant gastric ulcer with a high degree of accuracy.

The first two statements will play a role in our further considerations. The last statement, with which I fully agree, is of importance. In contrast with the general opinion, this differential diagnosis will usually be possible if all criteria are carefully considered, especially the gastroscopic findings. However, I shall not discuss in detail the roentgenologic and gastroscopic differential criteria between benign and malignant ulcer

In my opinion the more difficult differential diagnosis is that between a diffusely infiltrative carcinoma and other infiltrative lesions, such as lymphoblastoma, syphilis, Hodgkin's disease, and hypertrophic gastritis; and this important differential diagnosis may be equally difficult for the X-ray and for the gastroscopic examination. These rare cases have in common the fact that doubts concerning the nature of the lesion occur either at X-ray examination, or at gastroscopy, or at surgical interference. Some of them have been described and pictured before (*19*). The question comes up, Are we able to ascertain the correct diagnosis by taking a biopsy at the gastroscopic observation? Technically, this is no longer out of question. Kenamore, of St. Louis, invented a biopsy forceps to be attached to my flexible gastroscope. It has not yet been tried out in many cases, and I am afraid to recommend its routine use because I am sure that gastroscopy with this attachment would no longer be the safe procedure

which it is now, and that we should encounter mishaps which might discredit the important gastroscopic method. Nevertheless, in the hands of experts, gastroscopic biopsy could be considered. This question, however, remains to be settled.

Coming to the end of this section, I hope I have shown that as a rule gastric carcinoma can be discovered with a high degree of certainty by the roentgenologic or gastroscopic methods, that the differential diagnosis between carcinomatous and benign ulcers usually can be made quite definitely, and that there remain only a few diffusely infiltrative lesions which present difficulties.

If we are now able to diagnose practically every gastric carcinoma in which special anatomic methods are employed, does not this fact improve our therapeutic results decisively? I am afraid that this question is to be answered "No.' The great majority of cases we see are advanced cases, cases in which the carcinoma present cannot be called a small one, and the pessimistic data given to you before apply to most of these cases. We certainly can now boast that we do not overlook any longer the disease itself. But the situation as a whole has not become a much brighter one. If we ask why, we come to the question of the really "early" diagnosis of a gastric carcinoma.

VALUE OF EARLY DIAGNOSIS

Various definitions have been used for the expression "early diagnosis," and I myself have used two different definitions at different occasions (*20*, *21*). We might call an early diagnosis the diagnosis of a carcinoma in which a permanent cure becomes possible, regardless of its size; or, we may use the expression "early diagnosis" only for carcinomas of very small size, regardless of the later prognosis. I suggest using, in our present discussion, only the latter definition. Carcinomas of any size, which permit a permanent surgical cure could be called curable carcinomas, and the words "early diagnosis" would then be reserved for very small carcinomas. Now naturally it is impossible to draw a line between very small carcinomas and carcinomas of medium size, and I am reluctant to give definite measurements for this purpose. It has to be stated that early diagnosis of gastric carcinomas is rare. Why? There are two reasons. It has been contended, as you know, that most patients suffering from gastric carcinoma do not develop any symptoms until the carcinoma has reached a rather large size. I will show later that this is not quite correct, but it is correct in so far as the carcinoma in itself certainly cannot possibly produce any symptoms when it is very small, involving only a few square centimeters of the gastric mucosa. Such cases will not be seen by the doctor, and the best diagnostic methods are in vain if they cannot be used. Later I want to show a way to overcome even this obstacle.

The second reason why we see so few early carcinomas of the stomach is that many patients who have initial symptoms such as lack of appetite, slight loss of weight, or mild epigastric distress, are unwilling to undergo immediately time-taking and expensive examinations. The average doctor who knows the average bad prognosis of gastric carcinoma will not press them too hard to submit themselves immediately to X-ray examination and to gastroscopy, although he should. He realizes that in most of these patients nothing will be found, and he fears that his reputation will be in danger if he induces his patients to sacrifice so much time and money without practical results. Yet if he knew that in the cases in which a carcinoma was discovered, a cure could be effected, his attitude would change. But unfortunately he most likely has not

seen during his life a single case of cure of gastric carcinoma; on the other hand, he has seen many failures. Therefore, you see that the problem is a psychological one. I am convinced that as long as most of our laparotomies performed for gastric carcinoma are failures insofar as the patient dies from his carcinoma in spite of any kind of surgery, we shall not have the cooperation either of the public opinion or of the physician, concerning early, thorough examination. Only if the average practitioner will become convinced that laparotomy when recommended by the surgeon will lead to a success in a high percentage of all cases, will his attitude change. I have tried to explain the present attitude of patients and doctors, but naturally I shall not try to excuse them. There are patients whose lives can be saved, and their lives must be saved by all means. It is unjustifiable to delay a complete examination if there is even a slight chance of saving the life of the patient. But this is a problem which concerns the suggestions given at the universities and the medical schools and by our leading medical periodicals. It is not a question for a public health program. Our problem is, *Is it possible to find a way to determine the prognosis of gastric carcinomas in advance so that surgical failure can be avoided with a high degree of probability* and so that all the anxiety, disappointed hope, financial burden on the part of the patient, and the impaired reputation of the physician can be avoided?

CLASSIFICATION OF GASTRIC CARCINOMAS

In a recent discussion on gastric carcinoma one of our pathologists, Dr. Paul Steiner, stated—in my opinion quite correctly—that our knowledge of gastric carcinoma is inadequate. We are, he said, at about the same stage with gastric carcinoma as that of brain tumors before some neuropathologists and neurosurgeons, especially Bailey, began to classify the brain tumors and to try to treat these tumors according to the classification. It seems to me that this would be the proper procedure in gastric carcinoma, also. Now we do not differentiate between the prognosis of different forms of gastric carcinoma—we treat all of them in the same way. If we could find a *classification according to the surgical prognosis* so that a certain type would give on the average a good surgical outlook, another type on the average a very bad outlook, the problem as mentioned before would be changed, and I believe that the question of classification of gastric carcinoma should be one of the most important problems of research in the future. Closer cooperation among practitioners, surgeons, roentgenologists, gastroscopists, and pathologists over a long period of years, a most careful work-up of every case and especially of the pathological material obtained will be necessary. Obviously the usual microscopic criteria of gastric carcinoma are not of decisive value for the prognosis. Cures may be obtained in adenocarcinomas and in medullary carcinomas, as well.

Microscopic grading of carcinomas approximately according to the criteria of Broders (*22*) has perhaps greater value. And this might be done in gastroscopic biopsies before surgery. But I doubt whether this grading is a useful procedure. Grades 1 and 2 carcinomas are very rare in the stomach: and if they alone would give a good prognosis, the outlook would be a very dark one indeed. For more than 10 years I have had the definite impression that it is not the microscopic structure upon which the final prognosis of a gastric carcinoma will depend. In 1929 I observed the case of an exceptionally small pyloric tumor which, grossly, did not show any sharp demarcation and

was an invading type of carcinoma. However, the outstanding pathologist who examined this tumor microscopically stated that it consisted of tubules of so regular structure that he was inclined to diagnose a benign tumor; this was a grade 1 carcinoma. Nevertheless, the patient developed mucosal metastases 4 months later and died a short time after that from generalized carcinomatosis. From that time on I had the growing impression that the microscopic type of a gastric carcinoma is less decisive for the final prognosis than its macroscopic character.

Borrmann (*23, p. 865*), in his outstanding chapter on gastric tumors in the Henke-Lubarsch Handbook of Special Pathology, has given a macroscopic classification of gastric carcinoma which is now widely accepted and which is used everywhere in the gastroscopic description of gastric tumors. These types can be recognized in the gross specimen; they can be recognized easily at gastroscopic examination, if the whole circumference of the tumor becomes visible; and they can be recognized sometimes at X-ray examination, although the indirect conclusions drawn from even the best relief pictures do not permit statements so definite as does the gastroscopic observation. In order to recognize these macroscopic types, gastroscopy as a rule is by far superior to the X-ray examination; but in some cases X-ray may be superior to gastroscopy. The first gross type of gastric carcinoma is the polypoid carcinoma (pl. *1, B*). This is a sharply limited growth, often looking like a mushroom with overhanging edge. Its surface presents numerous nodes and nodules which are usually of different size. Only at a later stage will ulceration of this surface develop. The mucosa surrounding this type of tumor is often thoroughly atrophic. This type is not a frequent one. According to my own statistics it is found in 2.9 percent of all gastric carcinomas if the cardia carcinomas are omitted. In my experience, this type grows slowly and it seems that it never changes into another type, but remains polypoid and sharply limited. Microscopically, the tumors of this group usually are well-differentiated adenocarcinomas, but sometimes other microscopic forms, even medullary carcinomas, may be found. Figure 16 is the X-ray picture of a rather famous case (*24*) of a type I carcinoma developing in the atrophic gastritis of pernicious anemia. Figure 17 shows the gross specimen. Microscopically, the tumor could be considered as a grade 3 (fig. 18); nevertheless, this patient is still alive after 6 years.

FIGURE 16.—X-ray picture of a type I carcinoma that developed in the atrophic gastritis of a case of pernicious anemia. (From Cecil's Textbook of Medicine, p. 755. Reproduced through the courtesy of Walter Lincoln Palmer, author of the chapter from which the figure is taken; Russell Cecil, the editor; and W. B. Saunders Co., Philadelphia, publisher.)

The type II carcinoma is a very important form. (See pl. 1, *C*.) It is found in 17.6 percent of all cases. It is an ulcer surrounded by an elevated wall. This wall has a steep slope toward the surrounding mucosa and is sharply demarcated all

around against the surrounding mucosa. The floor sometimes shows necrotic material of all colors, brown, purple, gray, dark red, or white. The dark-red color of the wall may be in marked contrast to the pale color of the surrounding mucosa. In my experience this type of tumor remains sharply limited even if it grows. The thickness of the wall may double in 1 week, but the tumor does not become infiltrative. The fact that many of these tumors are sharply limited from the beginning and remain sharply limited is rather amazing and important. It is amazing because the microscopic structure of these carcinomas is not uniform. Figure 19 shows a type II carcinoma. The gross specimen is seen in figure 20. Microscopically (fig. 21), there is an absolutely sharp demarcation between the tumor and the surrounding mucosa, and yet the tumor is not a highly differentiated one. To me the startling point about these type II carcinomas is that they develop metastases only at a late stage and that their removal may lead to an extremely satisfactory end result, to cures of long duration, if the operation can be performed at not too late a moment. These are the well-known tumors which may reach the size of a fist, which can easily be palpated through the abdominal wall, and which are definitely movable. Sometimes this form may be recognized at X-ray examination, also. Carcinomas giving the so-called meniscus sign of Carman (*25*) are usually type II carcinomas (fig. 22), but naturally the gastroscopic diagnosis is more convincing and more reliable than the X-ray diagnosis. The type II carcinoma may be found in practically every place of the stomach, and in my opinion the final prognosis does not depend upon its site. The meniscus-sign carcinoma of figure 22 was found almost immediately below the cardia, and at gastroscopy the sharply limited wall was seen. Gastrectomy led to a 5-year cure.

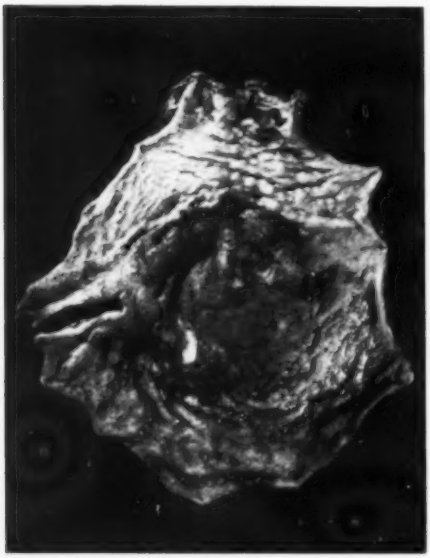


FIGURE 17.—Gross specimen of type I carcinoma. Same case as that shown in figure 16.

FIGURE 18.—Grade 3 carcinoma. Same case as that shown in figures 16 and 17.

FIGURE 19.—Gastroscopic picture of a type II carcinoma. A large ulcer is seen in the center, surrounded by a high nodular wall, sharply limited all around, and in the original view, dark red in contrast with the pale surrounding mucosa.

FIGURE 21.—Microscopic section through the edge of the type II carcinoma shown in figures 19 and 20. The gastric mucosa seen in the lower right quadrant is perfectly normal and does not contain any carcinomatous cells. The carcinomatous wall starts abruptly. The tumor is not very well differentiated.

In the type III carcinoma of Borrmann an ulcer is also found (fig. 23), which has a wall, but the wall is found only at one side of the ulcer. There is a more gradual transition of the wall. The ulcer itself, although sharply limited at one side, blends diffusely at the other side. This type III carcinoma occurs in 16.3 percent of all cases. Again the microscopic pictures are not typical.

The type IV carcinoma of Borrmann is the diffuse infiltrating type, which unfortunately occurs in 63.2 percent. No sharp limit will be found anywhere toward the normal gastric mucosa, either with the eye or at palpation; and sometimes the entire stomach may be infiltrated. In figure 24 a typical, stiff, nodular infiltration is seen which involved the whole stomach

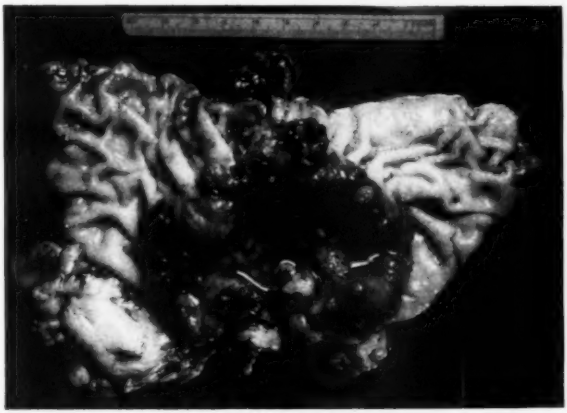


FIGURE 20.—Gross specimen of the type II carcinoma seen in figure 19.

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almost 2 years before the patient died. Within this infiltration ulcers may develop, shallow ones or deep ones. (See pl. 1, *D*.) They never show the sharp edge of the the typical benign ulcer. Diffuse infiltration of the gastric wall leading to a typical leather-bottle stomach is better diagnosed by X-ray than by gastroscopy (fig. 25). The type IV carcinomas seem not to be very favorable tumors. I myself have never seen a complete cure after the resection of such a tumor. But, naturally, the material I have is not sufficient to permit any definite conclusions.

FIGURE 22.—X-ray compression relief picture of a type II carcinoma immediately below the cardia, showing the meniscus sign of Carman. A collection of barium fills the ulcer crater and is surrounded by a dark area which interrupts the course of the normal gastric folds and which represents the wall of the tumor.

I hope that the knowledge of these four types will become of practical importance. In the extensive research which should be undertaken within the next decades concerning classification or typology of gastric carcinoma, not only the microscopic structure should be considered but also each gross specimen gained at operation or at autopsy should be inspected and photographed carefully for its macroscopic type. Whenever possible an attempt should be made to state the macroscopic type gastroscopically before the operation. I fully realize that it will be difficult to find out the relation between the types and the ultimate prognosis of the carcinoma. Many factors enter the picture which may seriously disturb our statistics. Early recurrence may happen after the extirpation of a type II carcinoma, if an incompetent surgeon cuts through the edge of the wall instead of through the noninvaded gastric mucosa. The cure of one of our type II patients in Chicago was spoiled because the patient suddenly died from a coronary occlusion. Although at autopsy no recurrence was found, this case cannot be recorded under cures obtained

surgically. Therefore, only an abundant wealth of material will overcome these statistical errors.

I mentioned before that there is no necessary relation between the macroscopic types and the microscopic grades. The material in which we succeeded in correlating microscopic sections with gastroscopic types is not abundant. We collected 39 cases in which such a study was possible. The data are given in table 1. There is no microscopic grade 1 in the material, and the 4 cases which would constitute a microscopic grade 2 are evenly distributed over the 4 types. It is interesting to note that many of the benign, sharply walled-off type II carcinomas belong microscopically to grade 4. I believe that the fact that there is no relation between the microscopic grades and the macroscopic types is established, and this fact should be borne in mind in our future research. It was a great satisfaction to me to learn by a personal communication that Pack, of New York, now simply classifies his carcinomas according to the gross types.

FIGURE 23.—Gastroscopic picture of a type III carcinoma. The floor of the carcinomatous ulcer is seen in the center of the picture. It blends without sharp limitation at the left side, while at the right side it is limited by a nodular wall. Antrum and pylorus are visible. A fold of the posterior wall is seen in the upper quadrant.

FIGURE 24.—Gastroscopic picture of a type IV carcinoma. Stiff, nodular infiltration throughout.

TABLE 1.—*Comparison between gross types and microscopic grades of 39 cases of gastric carcinoma*

Type (of Borrmann)	Grades				
	1	2	3	4	Total
	Number	*Number*	*Number*	*Number*	*Number*
I	.....	1	.....	.....	1
II	.....	1	3	9	13
III	.....	1	3	4	8
IV	.....	1	3	13	17
Total	0	4	9	26	39

The research on classification of gastric carcinoma according to its surgical prognosis should be in the hands of a central bureau, and I want to suggest the establishment of such a bureau for the collection of gross specimens, microscopic slides, and statistics about follow-ups. Such a central bureau would, after a few years, be able to come to a preliminary impression, and perhaps after 10 to 15 years to come to definite conclusions.

This presentation may have shown a possible way to discover *curable* forms of carcinoma. In the last part of this paper I shall show a way to discover real, *early* carcinomas of all types.

PRECANCEROUS CONDITIONS

It is a widely accepted theory now that gastric carcinomata do not develop on the soil of an entirely healthy gastric mucosa (*26*, *27*, *28*). Some European workers, especially Konjetzny (*29*), go so far as to contend that no gastric carcinoma ever develops in a perfectly normal gastric mucosa. It has been recognized that there are conditions of the gastric mucosa which have to be considered precancerous and which may later lead to the formation of gastric carcinoma (Ewing (*30*)). If this is so, then evidently a new approach has been found, and this concerns the truly early diagnosis of gastric carcinoma. Every gastric carcinoma has to start with a few malignant cells, and we cannot hope ever to discover a stage of gastric carcinoma in which only a few cells are malignant. But even in the most malignant growth there will be a stage of dividing malignant cells which have not yet invaded the lymph vessels but which are restricted to the gastric mucosa itself, forming a small pathological area which may be recognized at X-ray or at gastroscopic examination. Such truly early carcinomas, carcinomas of minimal size, cannot possibly cause any symptoms even if they are located in the pyloric region, and therefore, *a truly early diagnosis of such carcinomas of minimal size can be made only incidentally. We should attempt to find them when they do not cause any symptoms; and this can be done in those cases in which they develop on the soil of precancerous conditions by discovering these precancerous conditions and by watching such patients carefully by routine checks*, as I suggested in 1933 (*31*).

FIGURE 25.—X-ray picture of a typical leather-bottle stomach. Note the enlarged end of the esophagus and the shrunken, entirely rigid stomach. (Reproduced through the courtesy of Walter Lincoln Palmer, author of chapter from which figure is taken; Russell Cecil, the editor; and W. B. Saunders Co., Philadelphia, publisher.)

I am inclined to believe that there are carcinomas which have no precancerous conditions, but I agree that the great majority of carcinomas develop on a pathological soil.

What are the precancerous conditions? Three diseases have been considered forerunners of gastric carcinoma: (1) Gastric ulcer; (2) benign gastric polyp; and (3) chronic atrophic gastritis.

Let me dismiss gastric ulcer as a forerunner of gastric carcinoma with a few words. I simply do not believe—and many other experienced gastroenterologists concur with this opinion (*18*)—that gastric ulcer ever develops into a gastric carcinoma. It is true that 3 to 4 percent of all adults die from gastric carcinoma, and therefore it is to be expected that 3 to 4 percent of all ulcer patients will develop a gastric cancer also; but then the causal connection is hard to establish, and I agree fully with Palmer (*18*), who says that the existence of carcinomatous degeneration in benign ulcer remains to be proved con-

clusively. Most gastroenterologists who watch their ulcer patients over a period of several decades carefully have never seen such an ulcer develop into a carcinoma. To quote Palmer again, peptic ulceration of carcinoma may produce a lesion grossly indistinguishable from benign ulcer, so that, in my opinion, a carcinomatous ulcer is malignant from the very beginning. However this may be, we are accustomed to watch our ulcer patients carefully anyway, and I believe that the development of a carcinoma in an ulcer-containing stomach will not be overlooked so easily. Preventive resection of benign ulcer, however, is not justifiable.

The second disease to be considered, the benign gastric polyp (*32*, *33*), has been proved more frequent than we had thought until a short time ago. We find at gastroscopic examination three types of polyps: the inflammatory pseudopolyp, growing on the soil of atrophic gastritis; the adenomatous polyp (pl. 1, *A*), microscopically a real tumor (if it is rather large it may be seen by X-ray examination also (fig. 26)); and, finally, the rare hyperplastic polyp which microscopically consists of the elements of the gastric mucosa. Probably all these forms have a significant relation

FIGURE 26.—X-ray relief compression picture of a rather large polyp of the pylorus.

to the development of gastric carcinoma. In figure 27 a benign polyp and a type II carcinoma are seen in the same section. If we find a polyp incidentally, we extirpate it surgically or watch its bearer carefully. But I believe that, practically, in a systematic fight against gastric cancer, this disease will play a minor role.

But the really important forerunner of gastric carcinoma, which requires general consideration by the National Cancer Institute, is chronic atrophic gastritis, a very frequent disease. I believe it is the chief accomplishment of gastroscopy to permit us the definite diagnosis of chronic atrophic

FIGURE 27.—Microscopic section showing a benign polyp and a carcinoma together. At the right side of the field is the polyp, and at the left side an undifferentiated, but grossly type II carcinoma.

gastritis. Atrophic gastritis consists of a thinning of gastric mucosa, the glandular apparatus of which disappears slowly and is replaced by cellular infiltration (*34, 35*). The epithelium will often show the transition into intestinal type of epithelium with many goblet cells. The normal gastric mucosa is demonstrated in plate 1, *A*. Typical atrophic gastritis will be found in plate 1, *B*. Thinning and graying of the mucosa is seen, with the blood vessels becoming visible. And on the soil of this disease gastric carcinoma may develop.

This statement seems to be in contradiction to the old conception that gastric carcinoma usually develops in an entirely healthy individual, but in the light of recent investigation it seems that this old conception is true only for some cases. Kapp (*36*), of Basel, Switzerland, found that 13.4 percent of his cases of gastritis later developed into carcinoma. The figure of Usland (*37*), of Trondheim, Norway, is 15 percent, and this incidence is about three times that of gastric carcinoma in general.

Patients suffering from atrophic gastritis (*38*) sometimes have long periods in which they are free from symptoms, but usually they complain of minor epigastric distress, pressure, belching, bleating, or pain. But their general symptoms—extreme fatigue, headache, nervousness, numbness, and tingling of the limbs—are more characteristic. Only the gastroscopic picture is diagnostic, and this is one of the chief reasons why we need gastroscopy as a routine method. If it is true that patients with atrophic gastritis have three times the chance of developing a gastric carcinoma than other healthy adults, then it is our obvious duty to diagnose this disease as early as possible, and to watch these patients closely by frequent X-ray and gastroscopic examinations. With this procedure I believe we shall be able to find incidentally small carcinomas which cause no symptoms. This, then, would be the truly early diagnosis of gastric carcinoma. And I shall now present briefly three cases which will prove that such an incidental diagnosis is possible.

In a surgeon 58 years of age who had suffered for 20 years from abdominal pain, belching, and pressure, and who had had a histamine-proved anacidity for 8 years, a small filling defect was found at an occasional X-ray examination. Unfortunately this was misinterpreted as a spasm, and it was only when after 3 years this filling defect grew, that the patient submitted himself for gastroscopy. It is entirely obvious that earlier gastroscopy and probably careful X-ray relief technique would have discovered the small type I tumor 3 years before its actual discovery. The gastroscopic picture will be found in plate 1, *B*. It is a typical type I carcinoma, and the mucosa is thoroughly atrophic. There is no doubt that this patient had had an atrophic gastritis for at least 8 years, and that this tumor had been discovered incidentally. The microscopic section shows beautifully the transition of the atrophic mucosa into adenomatous tissue and into carcinoma (fig. 28). The patient is still alive, 2 years and 9 months after the operation, and without recurrence.

The second case does not show the connection between atrophic gastritis and carcinoma so convincingly, but it is striking because a minimal-sized carcinoma was discovered accidentally. The patient had suffered from epigastric distress and poor appetite for 1 year, and I believe that these symptoms were all due to the atrophic gastritis found at later microscopic examination. He had the usual complete check-up in our clinic, and Dr. Templeton was able to demonstrate a fleck suggestive of pyloric ulcer. The gastroscopic examination did not permit any doubt that this

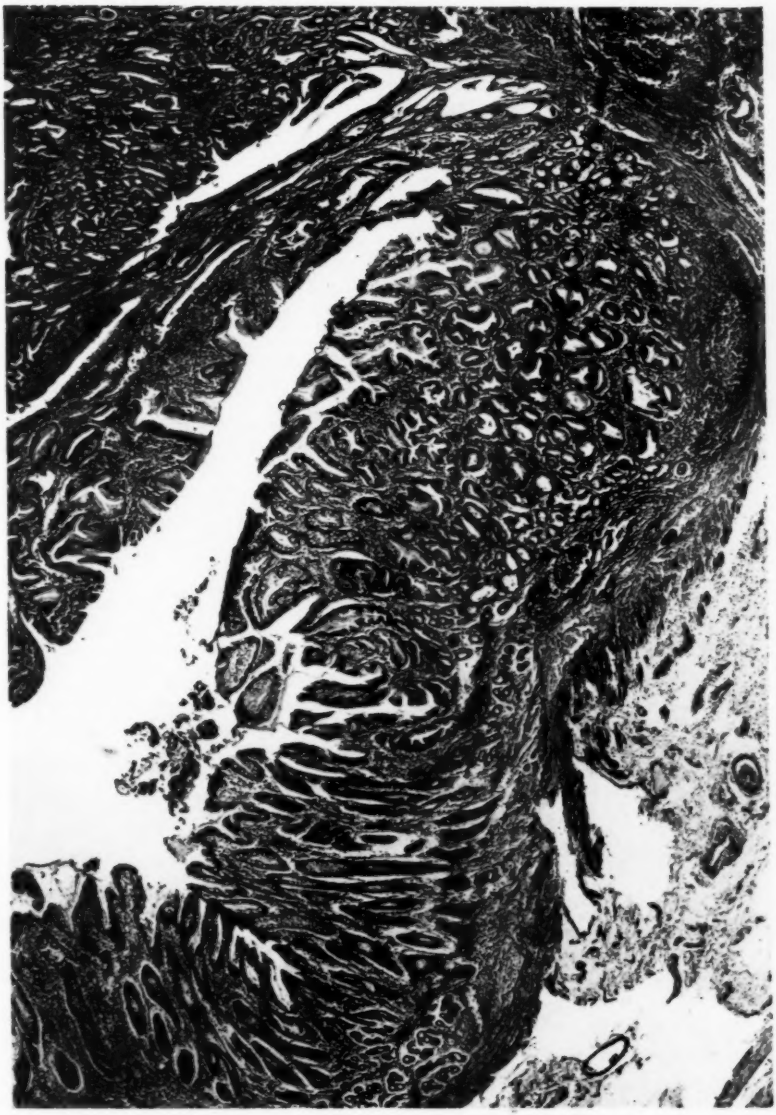

FIGURE 28.—Photomicrograph of a type I carcinoma developing on the soil of atrophic gastritis. The gastroscopic picture is shown in plate 1, *B*. In the microscopic section, the transition from atrophic gastritis into tumor tissue is well demonstrated. At the left, there is definite atrophic gastritis, disappearance of the glands, deepening of the crypts, cellular infiltration, and appearance of goblet cells. In the center, irregular adenomatous tissue is seen, part of it being still covered by an intestinal type of surface epithelium. At the right, the mushroom-like overhanging carcinoma has developed.

was a very small pyloric carcinoma (fig. 29) within an area of atrophic gastritis. The carcinoma found microscopically was

FIGURE 29.—Gastroscopic picture of an unusually small carcinoma within the pylorus. Note the distorted shape of the pyloric hole and the whitish ulcer area. A circular wave is seen migrating across the antrum toward the stiff pylorus.

FIGURE 31.—Gastroscopic picture of a small type III carcinoma, discovered incidentally at the routine examination of a patient suffering from pernicious anemia.

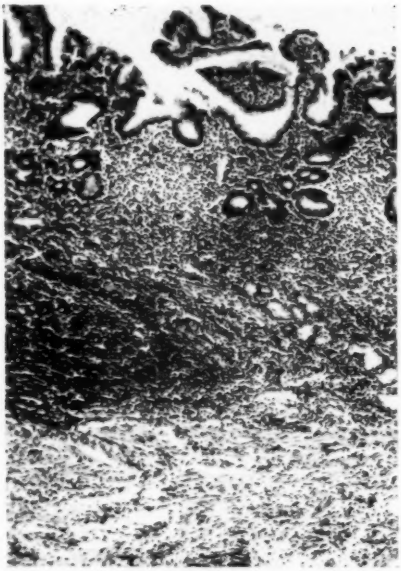

FIGURE 32.—Microscopic section through the mucosa of same patient as in figure 31. The severe atrophic gastritis is typical for pernicious anemia. There is no mere atrophy present. The enlargement of the lymph follicles, the splitting-up of the muscularis mucosae, the proliferative processes of the surface epithelium all speak in favor of an inflammatory process.

the smallest I have ever seen. Its width was 8 mm., and its depth 2 mm. (fig. 30). The microscopic examination of the adjacent mucosa showed extensive atrophy.

The last case is that of a patient suffering from pernicious anemia who presented himself for a check-up. At X-ray exami-

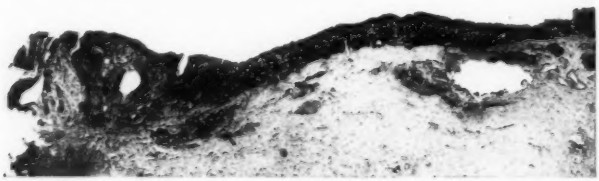

FIGURE 30.—Microscopic section through the small carcinoma shown in figure 29. The arrow indicates its greatest depth, 2 mm., below the surface.

nation nothing was found. At gastroscopy the usual atrophic mucosa of pernicious anemia was seen, and when the gastroscope was rotated in the middle portion of the stomach, a tumor wall was seen (fig. 31). It was a typical type III carcinoma. The microscopic examination revealed adenocarcinoma, lying in the severe atrophic gastritis (fig. 32) characteristic of pernicious anemia.

CONCLUSIONS

1. The modern development of the X-ray relief method and of gastroscopy permits the recognition of almost every gastric carcinoma, even of very small size.

2. Roentgenologists and gastroscopists must be thoroughly trained in order to be able to diagnose gastric carcinomas of minimal size.

3. The differential diagnosis of diffusely infiltrative lesions, carcinoma, lymphoblastoma, Hodgkin's disease, syphilis, and hypertrophic gastritis may be very difficult. It remains to be seen whether or not gastroscopic biopsy will be useful in this differential diagnosis.

4. Failure to advise X-ray examination and gastroscopy promptly in patients with apparently minor digestive disturbances must be looked upon as inexcusable.

5. At the present time, surgery must be advised for every patient in whom a gastric carcinoma has been discovered, if no metastases are present, and if the general condition of the patient is not a hopeless one. This situation, however, is not a satisfactory one from the psychological viewpoint.

6. Classification of gastric carcinomas according to their surgical prognosis should be tried. At the moment it seems that the macroscopic type will be more important for the prognosis than the microscopic type. Extensive research, using a wealth of material to settle this question, is recommended. The establishment of a central bureau for such purposes is proposed.

7. Of the three alleged precancerous conditions—benign gastric ulcer, benign gastric polyp, and chronic atrophic gastritis—the third one is the most important. For its early discovery, gastroscopy should be widely used, and patients in whom it is found should be watched carefully by routine X-ray and gastroscopic checks. In this way very small carcinomas may be diagnosed even before symptoms appear.

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DISCUSSION

Chairman Smith: I will ask Dr. Ewing to open the discussion.

Dr. Ewing: I would commend Dr. Schindler very highly for his attack on the problem and for his very competent discussion of a very important subject. I like especially his realism and his frank statements of the difficulties of the subject. I share that gloomy attitude toward the control of gastric cancer. I feel, however, that there are encouraging features of the subject. I think that gastric cancer, on the whole, is not among the most malignant varieties that we have to deal with, much less malignant than mammary cancer, and a considerable variety of cases fall into the group of very slow growing cancer, so that from many standpoints our present gloomy outlook may be transformed, perhaps, by advances in our knowledge of the disease.

I think Dr. Schindler has put together more information in a shorter time than I

ever saw, along with very numerous microphotographs without any confusion, and it was really a remarkable exhibition. I congratulate him.

By placing the cure rate of gastric cancer at 1.9 percent, which is probably too high for the general population, Dr. Schindler indicates that there has been little real progress in the last 30 years in the general control of this disease. Yet there has been very much progress in many directions, and mainly in the development of surgical technique, earlier diagnosis, and the provision of facilities for treatment. If we can develop a broad point of view toward the whole problem of gastric cancer, we may approach the subject from many standpoints and make a definite impression upon the death rate of this disease. Progress is seen especially in the fact that today, by the cooperation of the clinician, radiologist, gastroscopist, and surgeon, it is possible to recognize the great majority, indeed almost all, of gastric cancers, even in the early stages. It is most important to emphasize the fact that this result is possible only in the hands of experts and may not be expected in the average clinic.

Dr. Schindler has demonstrated in a very convincing manner that the gastroscope is of great value in this field. I might recall the fact that in 1920 Janeway was thinking of this matter and was making considerable progress by a rather crude instrument in the removal of portions of gastric lesions of a questionable nature and making positive diagnoses from biopsies. I do not see very much reference, in Dr. Schindler's report on gastroscopy, to the facility with which he can and the frequency with which he does take material for microscopic examinations.

I am quite impressed, as a general pathologist, with the superior conditions under which the gastroscope works over any other method of examining the stomach, because quite clearly when the lesion is in the living body and there is a circulation and you can observe all the various colors and shades and irregularities in the surface examined, you have features which are not provided anywhere else—not even in the surgical operation does the surgeon observe that. I think it is this fact which guarantees the soundness of the principles of gastroscopy and will assure its further development.

On the whole, the most impressive thing I get from the scope of this paper and the enormous number of details discussed is the necessity of specialization. I don't think that any man could produce such a discussion who had not spent a number of years, indeed, perhaps a considerable portion of his life, immersed in these problems, and I think that points the way for the better organization of our treatment facilities.

I am particularly interested in the question of differential diagnosis. It would appear from the reports which Dr. Schindler has given and from my contact with surgeons in general that the diagnosis of gastric cancer is considered a comparatively simple matter. In the pathological laboratory we do not find it to be so. We are constantly encountering in the gastric mucous membrane, lesions which are very difficult to diagnose. You will recall how Cole, some years ago, submitted a series of cases which he had diagnosed as cancer on radiological evidence, and which the surgeons and some other persons had doubted, to 20 prominent pathologists, and got an almost even division of opinion regarding the lesions. It is true that they were somewhat atypical and that some of them were early, perhaps what would be called precancerous lesions, but the fact that 20 different pathologists were unable to decide on 6 different cases of gastric cancer shows that the problems of differential diagnosis, even in the straightforward cases, are by no means simple.

You will recall, too, that Krompecher, one of the most experienced pathologists in Europe, took about 8 years to reach the conclusion that all the cases of so-called benign pyloric stenosis and partial linitis plastica represented various stages of atrophic gastric cancer.

Of course, we always have that most alluring debate on the cancerous degeneration of ulcer. I agree with Dr. Schindler that cancerous transformation of peptic ulcer has never been satisfactorily proven. I have not, myself, seen at any time a clear case of cancerous degeneration of an ulcer. I have seen, however, many instances in which it was apparent that a pre-existing cancer was being digested and sometimes only small traces of it could be found. That reminds me that over 60 years ago there were some authorities who claimed that all gastric ulcers were excavated cancers. I believe that is going too far. However, I am not willing to assert that there is no cancerization of an ulcer. I would entertain the possibility, though I have not seen such a case.

On account of these great difficulties in diagnosis, and for many other reasons, I agree heartily with the earnest necessity of establishing a registry of gross material, clinical reports, and microscopic sections. That method has accomplished a great deal in several other specialties, and I think it is very greatly needed in this field. However, I would suggest New York as the location for this registry, or, as a compromise, we might choose Washington.

Now we come to the question of classification. Some people are very much inclined to depreciate the importance of classification of disease. Nevertheless, history shows that in many instances a careful classification of all types of a human disease is the first step toward progress. This has been especially true with reference to bone tumors, and it is very much needed in gastric cancer. I agree that Borrmann's classification is very wisely chosen and extremely serviceable for the surgeon, and I thought, was rather widely adopted. Being essentially a gross pathologist myself, I would naturally approve of the approach to classification of any group of diseases on gross pathologic anatomy. However, I am not prepared to discard altogether the value of microscopic grading.

I think that the cases in which Dr. Schindler and others have pointed out errors in conclusions drawn from microscopic structure merely demonstrate the lack of experience on the part of the pathologist, and no pathologist would think of establishing a prognosis on cell type alone. He would want all the information he could get. I feel, however, that where one has a classification and a microscopic section, the study of the microscopic section can be developed to a high value in the estimation of the prognosis.

I do not know that radiosensitivity will be discussed in any later paper in this symposium. I therefore wish at this moment to raise the question as to the possible value of estimates of radiosensitivity, because with the rapid development of radiation therapy in general and the skill of the electrical engineer in developing X-ray machines, i predict that radiosensitivity will occupy a definite place in the future discussions of the treatment of gastric cancer.

Personally, I have been looking at the types of gastric cancer from somewhat different points of view from those which Dr. Schindler and most surgeons and specialists have observed them. It seems to me that there is some ground for assuming that we are dealing with a number of really different diseases, and that any attempt to deal with all of these different diseases from one standpoint is undesirable. I have been looking at gastric can-

cer for many years from the etiological standpoint, and I think when you take that point of view, the whole subject becomes considerably illuminated.

I have ventured to suggest very briefly in a recent number of the Review of Gastroenterology some of the conclusions that I have drawn on that subject. May I briefly review them here.

There is a certain group of cancers of the stomach which develop from tissue rests. They are found in the submucosa. They give no symptoms; they are accidental findings; they are not numerous; but they are worth considering. There is an increasing feeling on the part of pathologists, myself included, that a certain group of gastric cancers are due to nonepithelial structures. We are thinking more and more of sympathicoblastomas of the stomach. We have seen one or two in the last 2 years. They occur also in the intestines. Some of these are atypical, highly malignant tumors, with very bad prognosis, and I am wondering if they do not have an entirely different origin from the ordinary grade IV cancer.

There is no use considering cancer of the stomach as developed from tissue rests in the submucosa as the same disease as an advanced ulcer occurring in an elderly subject on the basis of a chronic gastritis. The whole history and all the clinicopathological features of the case are utterly different.

In cancer arising from polyps, the problem of etiology is similar to that of gastrointestinal polyposis. I have always regarded this disease as somewhat specific, of a marked hereditary character, probably based upon different factors from the atrophic gastritis, and it should be investigated from this standpoint.

We come to the question of chronic gastritis. I should like to suggest that we regard hypertrophic and atrophic gastritis as different stages of one general pathological process, and call it chronic catarrhal gastritis. It is a well-known principle that in all mucous membranes catarrhal gastritis tends to become chronic, that it is often marked by hyperplastic changes, that in other cases the tendency toward atrophy is most marked, and that the hypertrophic stage is usually followed, if the case lasts long enough, with the atrophic stage. If we regard all these cases of hypertrophic and atrophic gastritis as phases of chronic catarrhal gastritis, I think this would clear up some of the difficulties we have in discussing the relation between lesions of hypertrophic and those of atrophic gastritis.

It is in the group of hypertrophic gastritis that I find most difficulty in determining whether or not the lesion is malignant, and it was in this particular group that the 20 famous pathologists whom Cole put on the gridiron failed to reach a conclusion. There were in these cases hypertrophic areas and atrophic areas in the same stomach. The suspicious lesions were in the hypertrophic areas, overgrowth, increase in the number, and change in the size and type of cells, and disturbance in the general structure of the glands. Here we have a group of lesions which I think are the real, frequent, precancerous lesions, and I agree with Dr. Schindler that it is highly important that we should try to discover these very early and attempt to treat them.

Here, I think, comes the question that Dr. Rhoads will discuss, as to the possible relation of vitamins to the gastric mucosa. We have already found that these atrophic lesions of the buccal mucosa extend down the esophagus and even into the stomach, and they are dependent upon nutritional factors, but no one would consider such a mode of approach for gastritis polyposa.

You would have an additional reason, then, for assuming that we have different diseases, and this great group falls in this field of chronic catarrhal gastritis.

Finally, I think that the subject of the histology of gastric cancer is still in its infancy, if it has really reached that point.

I am very much interested to know what happens to the different cells in the gastric structures. Most gastric cancers arise from altered duct cells, but there is a peculiar small cell cancer which arises from the chief cells of the acini. It seems to me very likely that the etiological factors in a cancer which picks out the acini must be different from those factors which affect the ducts in atrophic gastritis. The possible participation of the argentophile cells in gastric lesions has never been traced. I do not know of any contribution from any pathologist in that respect. Neither has much attention been paid to the fate of acid cells. I can just say that it seems to me we have not, as pathologists, paid very close attention to the modern points of view in the study of the ordinary morphology and histology of gastric cancer.

There is almost no end to the interesting phases of this subject. My conclusion is, on a general review of the subject, that progress in this field demands, first, as Dr. Schindler has stated and as his own career indicates, the necessity for the concentration of material and the developing of high specialization in the study of gastric cancer, and I hope to see, in certain institutions where such material can be brought together, efforts to concentrate that material and to develop real gastric cancer specialists. This applies to pathologists as well. In pathology we do not see enough of these diseases to get a broad view of the whole subject. When that is done, I think the opportunities for progress in the early diagnosis and treatment are very definitely improved. However, I do not think that anyone should deceive himself into thinking that any of the methods of curative medicine now at our disposal, even under the best circumstances, are going to affect definitely the recorded death rate from gastric cancer, and therefore that any serious program for the control of gastric cancer involves some broad scheme of cancer prevention.

I shall close by referring to Cramer's observation, which I think is fundamental, that statistical studies show that gastric cancer is dependent upon extrinsic factors connected with the dietary, and, I would now add, nutritional habits of the population, and that studies directed to this field by physicians and public health agencies, and the Federal Government also, might make a change in the dietary habits and nutritional conditions of our population and thus bring about a real reduction in the incidence of gastric cancer.

Chairman Smith: . . . Our discussion will be postponed until after luncheon.

FRIDAY AFTERNOON SESSION

OCTOBER 11, 1940

(Dr. Carl Voegtlin, chief, National Cancer Institute, presiding.)

Chairman Voegtlin: We still have some discussion from this morning's program, and I should like to call on Dr. Zinninger to discuss the paper by Dr. Schindler.

Dr. Zinninger: It was a very great privilege to hear Dr. Schindler's paper and to see his lantern slides, and I wish to take this opportunity to express my apprecia-

tion of his splendid presentation. He has undoubtedly made a great contribution to the diagnosis and treatment of gastric lesions by the introduction of his flexible gastroscope. At Cincinnati we have come to regard gastroscopic examinations as an essential part in the study of any gastric lesion, except far-advanced gastric carcinoma in which the diagnosis is clear without its use. We use it as a complement of, or as a supplement to the X-ray and other studies, but we still feel that the X-ray at the present time, in the hands of most doctors, is the most important single laboratory study for gastric carcinoma. This presupposes, of course, what we believe to be the case today—that most gastric cancers are diagnosed only in the late stages. This has certainly been our own experience. In the last 8 years at the Cincinnati General Hospital, 123 cases of cancer of the stomach have been diagnosed. Less than half of these were in such condition that they could be operated upon, and only about one-tenth were early enough to be treated by resection.

We have had no experience with gastrophotography or the removal of biopsy material through the gastroscope. I was happy to hear Dr. Schindler say that he did not regard these as of very great importance, because that has been our own belief.

The value of gastroscopy, especially in the early cases, we regard as very clearly established. I should like to emphasize a little more than Dr. Schindler has done, the necessity of having a well-trained gastroscopist. The ability to pass the instrument and look through it doesn't mean that the proper interpretation is going to be made of what is seen. We therefore believe that if you are trying to diagnose cases early, it is absolutely essential that the man behind the instrument should be exceedingly well trained and well qualified, not only to make a thorough inspection, but also to recognize and differentiate benign from malignant lesions. Such proficiency in gastroscopy can be gained only by wide experience and by following one's cases to the operating room or to the autopsy room and comparing the gross and microscopic appearances of the lesion with the gastroscopic picture, and then attempting to correlate them.

Dr. Leon Schiff has been doing our gastroscopy in Cincinnati for some time, and I have been privileged to see the gastric picture before operation in many of the cases that I have subsequently operated upon, and then to see the gross and microscopic pathology and histology after the resection. Dr. Schiff has pointed out to me the differences gastroscopically between benign and malignant lesions, but he has also shown me some of the difficulties of interpretation. One of the great difficulties of differential diagnosis is between gastric carcinoma and other neoplasm of the stomach, two cases that I remember particularly well being an ulcerative neurinoma and a lymphosarcoma, both of which were thought to be carcinoma, gastroscopically.

The passage of the gastroscope is not without certain dangers. In a series approximating a thousand cases, we have had one instance in which the gastroscope has apparently torn a hole in the stomach. This was an outpatient. There was some difficulty experienced during the gastroscopy—not a great deal. The patient left the hospital, and about a half hour later he had severe pain, returned to the hospital, and was found to have a hole through his stomach, which was repaired. He is still in the hospital, but he is progressing satisfactorily.

Regarding the classification and grading of gastric cancer, I am heartily in accord

with Dr. Schindler. For a number of years we have taught our students that gastric cancer should be classified according to its gross appearance rather than its histologic appearance. We have long believed, as have many others, that bulky polypoid carcinomas often offer a better end result after resection than do small, infiltrating lesions. This is in accordance with the findings in other parts of the gastrointestinal tract, notably in the cecum, and the sigmoid, and in the rectum.

I have a few slides of large microscopic sections of cancer of the stomach, cecum, and sigmoid that I should like to show.

(Slide) This is a large microscopic section of a carcinoma of the rectum, a very small lesion, but with rather marked extension into the surrounding tissues.

(Slide) The next one is a very bulky carcinoma of the rectum, with very little evidence of infiltration into the deep tissues or into the surrounding structures or the lymph nodes.

(Slide) Here is a polypoid carcinoma of the cecum. This was almost on the lip of the ileocecal valve. You see that it is largely an adenocarcinoma with small areas of colloid degeneration. This one also shows very little or no evidence of infiltration. (Slide) This is a large colloid carcinoma of the cecum also, with small areas of adenocarcinoma in it.

(Slide) This is a resection of the stomach. Here is the pylorus, this is the lesser curvature going up toward the cardia, and this is the greater curvature going up toward the fundus. This is quite a bulky carcinoma, as you can see, and it is infiltrating in its nature. However, it does not project upwards. Involvement of the glands is marked. You can see here it is adenomatous, here it is almost medullary in type, and here are areas where it is almost scirrhous.

(Slide) This is another resection of the stomach. As you can see this carcinoma is very similar to the last one. It is bulky; it is not projecting; it is infiltrating. It shows areas of adenomatous change, but much of it is also like medullary carcinoma.

These sections illustrate some of the difficulties in histologic grading, and also the fact that the large, bulky types may not infiltrate as much as the smaller ones.

Regarding radiosensitivity of carcinomas of the stomach, which Dr. Ewing mentioned, we have had such poor results with radiation of gastric carcinoma that we have practically abandoned it.

I cannot entirely agree with Dr. Schindler that gastric ulcer never becomes malignant. I do not believe that this change is a very frequent occurrence, but I believe that it does take place. However, it is about as difficult to prove that it does occur as to prove that it does not occur. In analogy with chronic ulceration elsewhere in the body, we know that carcinoma every now and then does develop in the edges of chronic ulcers, and every now and then we see a chronic ulcerative lesion of the stomach, in one or two quadrants of which you can find carcinoma, while the other quadrants show only the appearance of the chronic ulcer of the stomach.

In conclusion, I am exceedingly interested in Dr. Schindler's findings of relationship between gastritis and cancer, because a group of us at Cincinnati have been particularly interested in studying the probable relationships of these two lesions for some time. So far, we have not been able to prove anything very definite in regard to the relationship, but some of our findings in this connection will be presented tomorrow by Dr. Reid.

Chairman Voegtlin: Dr. Gordon McNeer.

Dr. McNeer: It would be hard to add anything to the discussion concerning Dr.

Schindler's paper or the brilliant work he has done in the past. However, I feel that there are a few things which I should like to discuss, and one of them is the question of differential diagnosis between benign and malignant gastric ulcer. I do not feel that we have been as successful in making such a differential diagnosis as has Dr. Schindler, and I should like to show a couple of films in discussing that problem.

We were talking about the difficulties of the diagnosis of gastric cancer, which brings up a problem such as this. (Slide) This slide depicts acanthosis nigricans, which was seen in a patient of ours and which was the only thing that pointed to the possibility of a diagnosis of gastric cancer. Radiographic studies were made which were particularly inconclusive. Gastroscopy was performed and revealed a carcinoma of the antrum, which was later resected.

(Slide) The next slide shows an ulcer at the incisura of the stomach, which is very irregular. It was just as irregular in the gastroscopic picture, in the radiographic picture, at the operating room before it was resected, and in the pathological laboratory. It was called by all a malignant ulcer, but on section proved to be perfectly benign.

(Slide) In the upper left corner of the next slide is a small niche on the lesser curvature side of the prepyloric segment. Looked at gastroscopically, the niche appeared benign. However, when the stomach was resected, the lesion proved to be carcinomatous.

(Slide) On the right of the following slide we have a perfect example of the great value of gastroscopy. From the picture alone, it would be difficult to tell whether we are dealing with gastric cancer or gastric ulcer in the prepyloric region. Examination by endoscopic means revealed a normal stomach, and therefore definitely placed the lesion in the duodenum. The lesion was therefore classed as benign, and a gastroenterostomy was performed instead of a resection of the stomach.

(Slide) On the left of this slide is what was thought to be a benign ulcer, and on the right a large crater which was thought to be malignant. We were unable to differentiate in either case, and again it took pathological study to prove the exact nature of the lesions. The one on the right proved to be benign, and the one on the left was a carcinoma.

(Slide) This slide is presented as a brilliant example of the value of gastroscopy. On the left is shown what appears to be a very extensive filling defect in the prepyloric region. This did not fill out in spite of a half hour of fluoroscopic examination. I was going to resect this the following day, and when I gastroscoped the patient to see how far up the lesion might extend, I saw nothing. After a week's bed rest for the patient, we took another gastrointestinal series and disclosed a perfectly obvious duodenal ulcer which caused a tremendous amount of spasm that simulated the roentgenologic picture of gastric cancer.

(Slide) The next picture shows spasm to such a degree that one might think that gastric cancer was involved instead of ordinary duodenal ulcer with spasm.

(Slide) The stomach shown here represents what might have happened had gastroscopy been employed earlier. The first X-rays of the stomach appeared normal, and the patient was classified as having no disease of the stomach. Then he went home, and his own doctor said that his gastric symptoms were so bad that he had better have another gastrointestinal series. In the next series, 6 months later, a defect was shown. Endoscopy would probably have shown this lesion at a very much earlier date.

(Slide) A lesion is shown here which we found on the anterior wall of the stomach which had been entirely missed by roentgenography. The interesting thing about this lesion is that it was so extensive, extending almost up to the cardia, that we had to perform total gastrectomy for its removal; and yet there was not a ripple or change in the pattern of the stomach shown by either fluoroscopy or by roentgenology.

(Slide) I just wanted to bring out an interesting point, which is a little discouraging when trying to get people in early for the treatment of gastric cancer. I was interested in studying a group of cancers in young subjects under 30 years of age, and so I studied all the collected cases in the literature and compared them with our patients at Memorial Hospital. We found that the average range of symptoms in those patients on whom operation was not performed was 10.3 months, and in those who underwent resection it was 15.9 months, that is, almost 6 months longer. Unfortunately the person who heeds the warnings of the possibility of impending gastric cancer all too often comes to you early as far as he is concerned, but actually comes late in the course of his disease.

I might say, in closing, that a plea for greater training of men in endoscopy and in gastroenterology and roentgenography seems to me by far the greatest need we have. Classification is truly important; but fundamentally there are only four types of gastric cancers, and those four types are pretty definite. If we can spend the time in training men to learn how to diagnose cancer of the stomach and how to treat it at an earlier stage in its progress, possibly we shall have rendered a great service to mankind.

Chairman Voegtlin: I think there will be opportunity in the next sessions to discuss this subject further in connection with clinical cancer service.

Over 30 years ago, MacCallum and Wells, among the pathologists, began to advocate the consideration of diseases on a physiological basis. This viewpoint has been shown to be productive in new knowledge, and for that reason the next paper will deal with recent work on the physiology and biochemistry of the stomach. Dr. Alexander Brunschwig, Professor of Surgery, University of Chicago, will present the paper.

Experimental Observations on Achlorhydria of Gastric Cancer [1]

By Alexander Brunschwig, *professor of surgery;* and Robert L. Schmitz and Richard Rasmussen, *research assistants, Department of Surgery and Medicine, University of Chicago Clinics*

Approximately 60 percent of patients with carcinoma of the stomach exhibit achlorhydria. In a study based upon some 70 specimens of cancerous stomachs removed at operation or necropsy, no correlation was possible between the site of the neoplasm, its size, and histologic type on the one hand, and the quality of gastric secretion as observed following the histamine test, on the other hand (*1*).

Studies of the proteolytic properties of achlorhydric juice from cancerous stomachs by means of Mett's tubes revealed a lowered concentration of pepsin content; but a similar reduction in pepsin content was observed in achlorhydric juices from patients not presenting carcinoma of the stomach. Kirsner, Nutter, and Palmer (*2*) studied electrometrically the pH of achlorhydric gastric juices from patients with carcinoma of the stomach and pernicious anemia. In 17 instances of the latter, the pH varied from 7.0 to 8.0; in 8 instances of carcinoma, it varied from 4.8 to 8.5. The significance of the greater variation in the latter group of patients is not now apparent.

Because of the rather frequent observation that achlorhydria existed in a cancerous stomach the microscopic appearance of whose fundic mucosa was not markedly altered, it was decided to test experimentally the hypothesis that such achlorhydria might be the result of a local preponderance of a gastric secretory depressant Previous reports of these studies have been published elsewhere (*3, 4*).

EXPERIMENTAL PROCEDURE

Such experiments were carried out in the classical manner employed by physiologists to test the effect of a given substance upon gastric secretion, by intravenous injection in a dog with a gastric pouch cannulated through the abdominal wall so that the secretions of the latter could be collected and analyzed at will. In the experiments performed in this study a variety of pouches were at first used, as shown in figure 1. The wedge and subtotal pouches were found to be most satisfactory as the secretion of smaller pouches is inconstant.

Two categories of test substances were employed (1) boiling 0.2 percent HCl extracts of cancerous and control stomachs and tissues, and (2) the juices from cancerous and control stomachs.

The animals employed were dogs varying in weight from 5 to 12 kg. which had been operated upon 1 or 2 months prior to use in the experiments. The animals had also been desensitized to extracts of human tissues by repeated injections of small doses of human-tissue extracts. In studies concerned with depressants of gastric secretion, the temperature factor is of great importance because an animal whose temperature increases rapidly as the result of injection of a foreign material will exhibit depression of gastric secretion and achlorhydria. Control studies showed that

[1] *This work was conducted under grants from the International Cancer Research Foundation, Philadelphia, Pa., and from the National Advisory Cancer Council of the United States Public Health Service, Washington, D. C.*

after repeated injections of pyrogenic extracts, the animals would finally reach a stage of relative immunity to such pyrogens and would not exhibit rises in temperature; or what is of equal importance, the gastric secretory mechanism would finally become resistant to temperature elevations and the volume of secretion and acidity of the juice would not be significantly depressed although an appreciable transitory fever would develop. In general, it was observed that in fresh animals a rise in rectal temperature to above 40.5°–40.6° C. would be accompanied by depression of gastric secretion and achlorhydria.

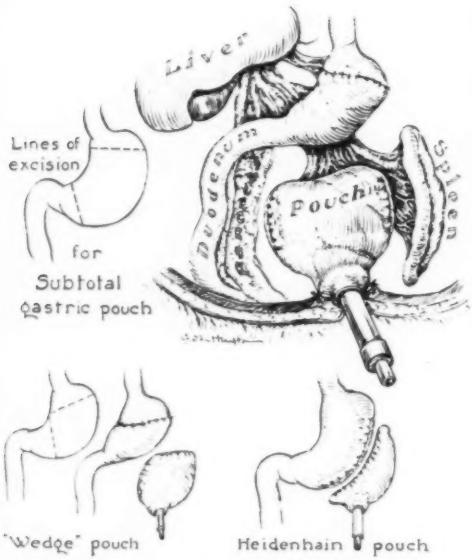

FIGURE 1.—Schematic illustrations showing types of gastric pouches used in dog. (Courtesy of Surgery, Gynecology, and Obstetrics.)

A typical experiment consisted of placing the dogs on a large table with free access to water and feeding them cooked lean meat. When the flow of gastric juice became adequate as seen in the glass Soxhlet flask suspended beneath the cannula leading from the pouch, the material to be tested was injected in an extremity vein. The volume and acidity of the pouch juice was then determined at 10-minute intervals. Feedings of meat were given at 30-to-40-minute intervals; and if the animals did not eat voluntarily, they were forcibly fed. Rectal temperature readings were made at intervals of 20 to 40 minutes for reasons stated above. Figure 2 shows a graph of a typical positive and control negative experiment.

Control studies showed that appreciable quantities of highly acid gastric juice were secreted for periods of several hours under the conditions outlined above when no injections were made. Since gastric secretory depressant effects were sought, the results were arbitrarily recorded as follows: +, depression of volume of secretion to 3 drops or less for two 10-minute periods or of a fall of free acid to 25 clinical units or less for one 10-minute period. A fall of free acid titer from say 70 or 100 to 40 or 50 clinical units was disregarded: ++, achlorhydria for 10 to 20 minutes: +++, achlorhydria from 30 to 50 minutes: ++++, achlorhydria for 1 hour or more. When no depression of pouch secretion occurred, the experiment was terminated 2½ hours after injection. When depression occurred there was usually a latent period of 30 to 90 minutes, sometimes longer; the experiment was then continued until free acid and volume of secretion returned to preinjection levels.

The extracts were prepared as follows: The gastric mucosa and carcinoma, if the latter was present, were stripped from the muscularis, cut into small pieces, pounded with sand, and extracted by addition of 50 cc. of 0.2 percent HCl per 12 gm. of tissue, boiled in a Kjeldahl flask for 10 minutes, and let stand overnight at room temperature. The tissue

fragments and sand were separated by centrifugation, and the cloudy fluid was neutralized with NaOH to litmus. When the latter step was performed, a flocculent precipitate formed. In one series of experiments the precipitate was shaken up into the supernatant fluid, and the mixture employed as a crude extract, being injected in an arbitrary dose of 1 cc. per kilo body weight.

Table 1 shows that the incidence of the gastric secretory depressant was significantly greater in achlorhydric cancerous-stomach extracts than in controls. A second series of experiments was performed in which the flocculent precipitate which forms upon initial neutralization of the extract was separated from the supernatant fluid by centrifugation, dried, and in doses of 100 to 300 mg. resuspended in 15 cc. of distilled water, and injected intravenously into the pouched dogs. The gastric secretory depressant was observed in both test and control samples

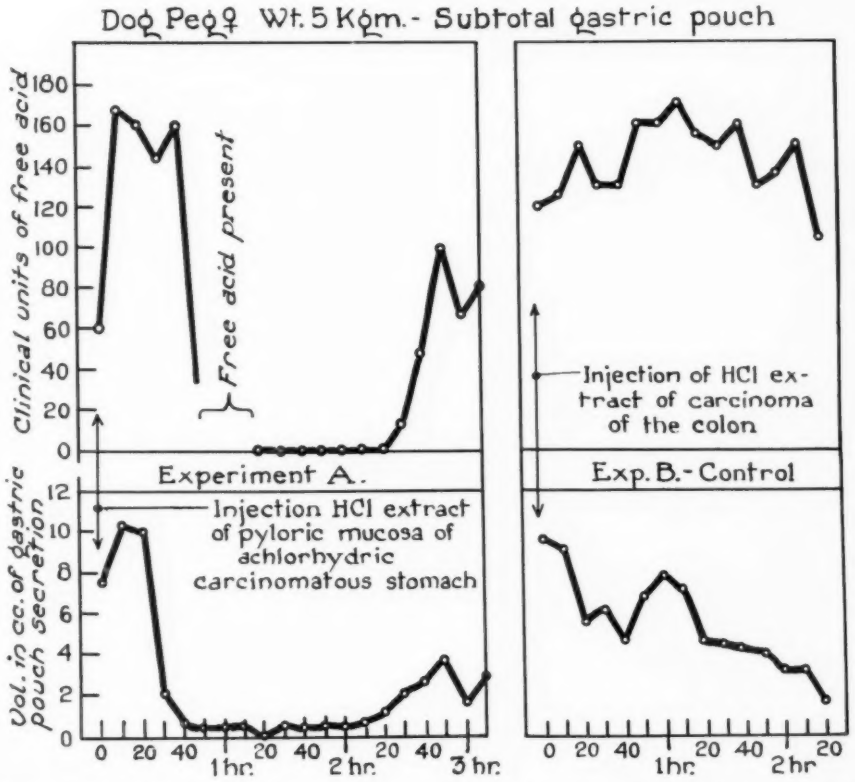

FIGURE 2.—Graph of a typical experiment showing transient suppression of gastric-pouch-secretion volume and achlorhydria following injection of 0.2 percent HCl extract of pyloric mucosa from achlorhydric carcinomatous stomach—dose of the latter 5 cc. intravenously. (Volume of secretion and titrations for free and combined HCl were made at 10-minute intervals. The pouch secretion was stimulated by feeding lean meat at intervals of 20 to 40 minutes throughout the experiment.)

TABLE 1.—*Injection of tissue extracts*

Source	0.2 percent HCl extract [1]			Dried precipitate of neutralized extract [2]		
	Positive samples	Negative samples	Percent positive	Positive samples	Negative samples	Percent positive
	Number	*Number*		*Number*	*Number*	
Achlorhydric carcinomatous stomachs	11	11	50	6	6	50
Acid-secreting carcinomatous stomachs	3	9	25	1	3	25
Stomachs from patients with carcinoma elsewhere	7	23	23	3	17	15
Stomachs from patients without malignant neoplasms	7	27	21	4	24	14
Carcinoma of colon	1	16	6			
Various benign and malignant neoplasms	6	54	10			
Colon mucosa adjacent to colon carcinoma	0	11	0			

[1] Dose employed: 1 cc. of extract (12 gm. of tissue to 50 cc. of 0.2 percent HCl) per kilo weight of animal.
[2] Dose employed: 100 to 200 mg. of precipitate resuspended in 10 cc. of water.

to be associated with the precipitate, and was not observed in the supernatant fluids. As shown also in table 1 the incidence of the gastric secretory depressant in extracts of achlorhydric cancerous stomachs remained the same when the dried precipitates were employed as when the whole crude extracts were injected.

Repeated injections of positive extracts resulted in a prolonged achlorhydria lasting 5 to 8 hours which was also shown to be histamine-fast, i. e., persistent in spite of subcutaneous or intramuscular injections of histamine.

Since the secretions of a parenchymatous tissue are in a sense, at least, a partial extract of that tissue, a series of experiments were conducted in which gastric juice obtained from patients by the usual procedure of histamine test for gastric juice was injected into the test animals under conditions similar to those described above in the experiments with tissue extracts. The results are summarized in table 2. If the juices obtained were acid, they were first neutralized by NaOH prior to injection. The arbitrary dose was 1 cc. of juice per kilo body weight of the animal.

Various attempts at isolation of the active secretory depressant were made from the juices, such as precipitation with phosphotungstic acid, salting out with ammonium sulphate or sodium chloride, absorption on carbon particles, etc., but these were all negative. However, the addition of 4 volumes of absolute alcohol to 1 volume of juice (neutralized, if acid) yielded a white flocculent precipitate which, when dried and injected into ani-

TABLE 2.—*Injection of juices*

[Juices containing free HCl were neutralized before injection]

Source	Whole juice [1]			80 percent alcohol precipitate [2]		
	Positive	Negative	Percent positive	Positive	Negative	Percent positive
	Number	*Number*		*Number*	*Number*	
Achlorhydric carcinomatous stomachs	21	6	78	5	4	55
Pernicious anemia	16	2	88	12	4	75
Achlorhydric stomachs—no carcinomata or pernicious anemia	7	18	28	9	15	38
Acid-secreting stomachs—no carcinomata or pernicious anemia	16	64	20	6	24	20
Carcinomatous stomachs secreting acid	2	10	17	1	3	25

[1] Dose: 1 cc. of juice per kilo weight of animal.
[2] Dose: 30 cc. of juice to which 120 cc. absolute alcohol was added. Precipitate was removed by centrifugation and injected into dogs weighing 8 to 10 kg.

mals by resuspension in water, contained the active principle if the latter was present in the original sample of juice. The doses employed in the latter experiments consisted of the precipitate from 10 to 30 cc. of juice injected into animals weighing 6 to 10 kg. Evidence was obtained to indicate that the gastric secretory depressant was not dializable through a cellophane membrane. Furthermore, the principle observed in the juices was heat labile, being destroyed by boiling for 5 minutes.

As in all biologic experiments employing crude test substances, the results were not always uniform. Thus, in employing the whole extract at least five separate experiments on at least two different dogs were performed; and a given sample was not tabulated as positive, i. e., containing the gastric secretory depressant, unless at least three positive experiments were obtained. In the experiments with juices, fewer tests were performed with each sample, and two clear-cut positive results were considered necessary to tabulate the juice as containing the gastric secretory depressant. Thus with some of the positive samples, some negative experiments were obtained.

DISCUSSION

A review of the accompanying tables shows that with the extracts of achlorhydric carcinomatous stomachs, a significantly higher incidence of gastric secretory depression was obtained than with the controls. While the latter experiments appeared adequate, other factors which might account for gastric secretory depression were nevertheless considered; and additional control experiments performed. In brief, these factors are as follows:

(1) Temperature induced in the animal by injection of foreign materials. This has been discussed above.

(2) Vomiting occurred at varying intervals in some cases following injections. Control experiments have shown that one gastric pouch secretion is induced by feeding; the emptying of the small stomach by vomiting does not result in a sudden and sharp decrease in pouch secretion or acidity of pouch juice. All animals were fed shortly after vomiting.

(3) Since it has been stated that marked depression of the carbon dioxide-combining power of the blood results in depression of the acidity of gastric secretion (*5*), samples of blood were withdrawn from the animals prior to and during a period of induced achlorhydria. There were no appreciable differences.

(4) A bacterial flora elaborating toxins which have a gastric secretory depressant action was also considered, and it was felt ruled out in view of the employment of extracts of highly necrotic colon-carcinoma extracts in experiments.

(5) Prolonged vasodilation could not account for the induced achlorhydrias observed since manometric blood-pressure readings taken from cannulated carotid arteries in anesthetized dogs did not exhibit more pronounced fall in blood pressure after injection of positive extracts than after injection of control extracts.

(6) Saliva, injected intravenously in dogs, was observed to result in some instances in gastric secretory depression and achlorhydria, but there was no correlation between this and the positive gastric juices. Furthermore, the patient's saliva contaminated all gastric juices obtained.

(7) Enterogastrone (*6*), the hormone formed primarily in the duodenum and responsible for the inhibition of gastric secretion following ingestion of fat, could hardly have accounted for the positive results observed above, since in the case of the extracts the stomach and not the duodenum was employed; and in the case of the gastric juices, no fat or any other

food had been taken during the night preceding the histamine tests. Additional control experiments were performed to show that in the dog under optimum conditions for production of enterogastrone, the latter does not appear in significant quantities in the gastric juice.

The significance of the rather high incidence of positive control experiments is not now apparent, and the question is now being investigated from the standpoint of such incidence being evidence of a normal chalone mechanism. A slight degree of purification of the stomach extracts resulted, as shown in table 1, in a slight reduction in the incidence of positive control experiments in some series. However, as shown in table 2, precipitation of the juices by 80 percent alcohol did not appear to alter this incidence; indeed it increased the incidence in the series of achlorhydric juices from patients not presenting gastric cancer or pernicious anemia. Possibly, this latter group of patients included some individual whose achlorhydria indicated the development of conditions favorable to gastric carcinogenesis.

The incidence of the gastric secretory depressant in achlorhydric juices from patients with pernicious anemia was found to be as high as or higher than in the achlorhydric juices from carcinomatous stomachs. This is of interest in view of the oft-repeated statements and studies in the literature to the effect that the incidence of benign and malignant neoplasms of the stomach is greater among patients with pernicious anemia, than among comparable age and sex groups in the population at large.

If only for purposes of discussion the hypothesis that achlorhydria in cancer of the stomach is often associated with a local preponderance of a gastric secretory depressant is accepted, the observations of Comfort and associates (*7*) that cancer of the stomach is often preceded for years by a decrease in gastric acidity might be interpreted as indicating that in some cases the local concentration of the gastric secretory depressant is associated in some way with the process of cancerization.

SUMMARY

1. Evidence is presented to indicate that the achlorhydria of cancerous stomachs is associated with a local concentration of a gastric secretory depressant which is demonstrated in extracts of achlorhydric cancerous stomachs and juices from such stomachs.

2. The gastric secretory depressant was also observed in achlorhydric juices from patients with pernicious anemia in incidence equal to that observed in achlorhydric juices from cancerous stomachs.

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DISCUSSION

Dr. Voegtlin: The discussion will be opened by Dr. Ivy.

Dr. Ivy: Mr. Chairman, Ladies, and Gentlemen: We have been following the work that Dr. Brunschwig and his associates have been doing, because for the last 20 years we have been attempting to produce achlorhydria in the stomach of the dog. Dr. Brunschwig seeks to explain the achlorhydria that occurs in the stomach of some patients with cancer, and we have been trying to discover how to produce achlorhydria with the idea in mind that we might use such knowledge in treating patients with peptic ulcer. We should like to have information regarding how the stomach forms its acid, so that we can turn the acid off and on, at will.

We first tried to produce permanent achlorhydria by injuring the gastric mucosa. In these studies we used hot water at 56° C., to coagulate certain albumins and cells. We used X-rays, and we used hydrogen peroxide. We were able to produce temporary achlorhydria by this means. For example, when we gave our animals an injection of histamine, they, instead of secreting water containing hydrochloric acid, secreted water containing sodium chloride. The volume output of secretion would increase in response to the histamine, but acid was not produced.

When we looked at the parietal cells in such stomachs, they appeared normal morphologically to us. We had injured or interfered with the mechanism concerned in the formation of hydrochloric acid.

We shall not be able to give a complete analytic discussion of this problem of achlorhydria until we know more regarding how the parietal cells form acid. To illustrate our relative ignorance, I shall give you an example of an experience regarding spontaneous achlorhydria in monkeys. From all of the monkeys that came into our medical school, we selected those that had achlorhydria after eating. We picked out some 15 or 16 such monkeys. Then we went over this group and picked out those that would not respond to histamine. Eight such animals did not respond to histamine. After proving that these animals did not have an anemia and failed to secrete acid after repeated histamine tests, we decided to try mecholyl, a parasympathetic stimulant. Some of them responded to mecholyl, and after we had injected 1 or 2 doses of mecholyl, all of the monkeys responded to histamine.

How can one explain an experience of that sort? We don't know enough yet about the mechanisms controlling the formation of acid by parietal cells to explain observations of that type.

When Dr. Brunschwig made his first report, we thought that he was probably extracting enterogastrone from the cancerous tissue. We can extract enterogastrone, a substance that inhibits both gastric secretion and motility, from the upper intestinal mucosa. Our extract is free of substances that have an effect upon blood pressure; it is free of pyogenic substances; it will not cause the animals to vomit. In assaying our extract I feel that we use a somewhat more rigid method than is being used by Dr. Brunschwig.

We use animals very much like his, with a pouch of the entire stomach and with the vagi cut. We inject histamine every 10 minutes until the pouch is secreting a uniform amount of acid, and then we inject our unknown. If it is active, the output of hydrochloric acid will decrease. We define 1 unit of enterogastrone as that amount of material which will reduce the hydrochloric acid output by 50 percent.

However, I have studied Dr. Brunschwig's data with considerable care in an attempt to find something wrong with it. We cannot criticize his interpretation of the data. The same is true of his experimental analysis of the problem. I believe Dr. Brunschwig has something.

Whether the active agent is enterogastrone, or whether it is a nonspecific substance liberated by the abnormal gastric mucosa, we cannot say.

In our physiologic tests, in which we applied fats to a pouch of the entire stomach in an attempt to inhibit motility and secretion, we have been unable to show that the gastric mucosa forms enterogastrone. Accordingly we have not made extracts of pyloric mucosa. In regard to the presence of Dr. Brunschwig's inhibitor in the gastric contents, it should be pointed out that if one perfuses the lumen of the upper intestine with acid or with sodium chloride solution, one obtains secretin in the perfusate. If enterogastrone is made by the atrophic gastric mucosa or by the pyloric mucosa in the presence of a cancer, it is possible that some enterogastrone can be found in the juice or in the contents of the stomach. Whether enterogastrone is identical with the inhibitory principle that Dr. Brunschwig has discovered will remain equivocal until we chemically isolate these active principles.

I hope that Dr. Brunschwig will continue with this work and will try to isolate his principle, because it may be a substance that will be useful in the treatment of peptic ulcer patients, particularly those patients who show a continuous hypersecretion of gastric juice. That is why we are spending so much time in our laboratory at the present time on the purification of enterogastrone and urogastrone. Urogastrone is a substance which is present in canine and human urine and which inhibits gastric secretion. The source of the urogastrone has not yet been determined. We have preliminary evidence indicating that it comes from the upper intestine. In most of our experiments in which we have removed the intestine to ascertain if the urogastrone disappears from the urine, we have also removed the pyloric antrum with the idea that that may be a source of the inhibitory substance in the urine. We have not completed this series of experiments, so we cannot say whether it is necessary to remove the pyloric antrum in order to observe complete disappearance of urogastrone from the dog's urine. In fact, we are not yet certain that pylorectomy and enterectomy always cause complete disappearance of urogastrone from the urine.

Chairman Voegtlin: Is there any further discussion of this paper?

* * *

The next paper is Hyperplastic and Neoplastic Lesions of the Stomach in Mice, by Dr. Harold L. Stewart, Senior Pathologist, National Cancer Institute, United States Public Health Service.

Hyperplastic and Neoplastic Lesions of the Stomach In Mice

By HAROLD L. STEWART, *senior pathologist, National Cancer Institute, National Institute of Health, United States Public Health Service*

The paucity of reports on experimental induction of gastric cancer in animals contrasts sharply with the frequency and importance of this lesion as it occurs in man.

This communication describes the pathological changes which occur spontaneously in the stomachs of strain I mice and presents some of the results of our experiments on the production of squamous carcinoma of the forestomach.

Most investigators, who have attempted to induce cancer of the stomach, have used the mouse or the rat as the experimental animal. Both of these animals possess a stomach composed of two chambers. The proximal portion, namely, the cardiac chamber, or forestomach, comprises two-thirds of the viscus and is lined by stratified squamous epithelium, continuous with that of the esophagus. The distal portion, or pyloric chamber, is separated from the upper squamous portion by a limiting ridge. This chamber is lined by glandular mucous membrane and is analogous to the stomach of man. From this it follows that two histologically distinct types of cancer of the stomach can theoretically be induced in mice and rats. In the forestomach a squamous-cell carcinoma might be produced which would be analogous histologically to squamous-cell carcinoma of the lower end of the esophagus in man. The pyloric chamber might yield adenocarcinoma which would correspond to the common gastric cancer of man.

The literature on experimental cancer of the stomach has been reviewed by Stewart and Andervont (*1*), Stewart (*2*), and Klein and Palmer (*3*). The latter publication is a detailed critical review with emphasis on the criteria which should be fulfilled before any lesion of the stomach can be considered as induced cancer. Klein and Palmer have rendered a real service to investigators in this field by their careful critical evaluation of the reported studies on this subject. No summary could do justice to this review, and the reader is referred to the original.[1]

All studies concerning the occurrence of spontaneous cancer in domestic, laboratory, and wild animals uniformly show that the stomach is a rare site of origin (Wells, Slye, and Holmes (*4*); Slye, Holmes, and Wells (*5*)). In more than 142,000 mice of the Slye stock which died of natural causes, Wells, Slye, and Holmes (*4*) reported 12 instances of gastric malignancy. These were distributed as follows: 8 squamous-cell carcinomas, 3 adenocarcinomas, and 1 sarcoma. In addition, there were 2 cases of adenoma, which lesions may have been early carcinoma. This listing represents all the examples of gastric cancer in the Slye stock of mice in over 20 years of observation. Their report, essentially confirmed by all other investigators, stresses the rarity of spontaneous gastric neoplasms in mice. In the laboratories of the Office of Cancer Investigations, United States Public Health Service, and of the National Cancer Institute during the past few years, thousands of post-mortem examinations were performed on mice of various strains, but not a single animal showed a spontaneous malignant tumor of the stomach. It

[1] *See p.* 559 *to* 584.

FIGURE 1.—Stomachs of four strain I mice. Each specimen of stomach was distended with fixative and cut into three portions. From left to right, the stomachs are from mice aged 2½, 6, 10, and 11 months, respectively. There is thickening and hypertrophy of the glandular mucous membrane of the stomach increasing with the age of the animal. Photograph of gross specimens.

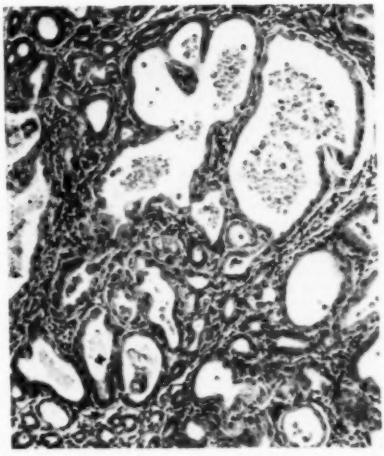

FIGURE 2.—Glandular mucosa of stomach of strain I mouse showing altered atypical acini. Photomicro × 150.

should be pointed out in this connection that many of these mice were autopsied before they had reached old age.

EXPERIMENTAL OBSERVATIONS

ADENOMATOUS LESION OF THE STOMACH IN MICE OF STRAIN I

A spontaneous adenomatous lesion in the pyloric chamber of the stomach in mice of strain I has been described by Andervont and Stewart (*6*) and Stewart and Andervont (*1*). The lesion occurred in virtually all mice of both sexes of this strain and was the chief cause of death. The lesion was characterized by adenomatous, hypertrophic, hyperplastic overgrowth of the glandular rugae of the pyloric mucosa. Degeneration of the glandular cells and infiltration of the mucosa and submucosa by inflammatory cells were present. These were associated with atypical glandular epithelium which showed limited penetration into the deeper gastric wall and blood vessels. The lesion made its appearance in the first 6 months of life and became pronounced in animals from 8 to 10 months of age. When pronounced, it was possible to detect the lesion clinically by palpation of the abdomen. The stomach became greatly enlarged, chiefly owing to the enlargement of the pyloric chamber. The forestomach was somewhat atrophied. Upon sectioning the stomach, the glandular mucous membrane of the pyloric chamber was found to be the seat of pronounced thickening and polypoid formation, so that the lumen of this portion of the stomach became considerably reduced in caliber (fig. 1). The hyperplastic areas in the glandular mucosa were symmetrically distributed and first made their appearance at the junction of the two gastric chambers. The thickened, atypical, mucous membrane partially encircled the esophageal opening and spread along both curvatures over the entire inner circumference of the proximal portion of the chamber, fading

FIGURE 3.—Wall of stomach of strain I mouse showing glandular mucosa above and muscular wall below. There is a solitary dilated acinus beneath the muscularis mucosa which extends through the muscular wall and is in contact with the serosa. Photograph × 100.

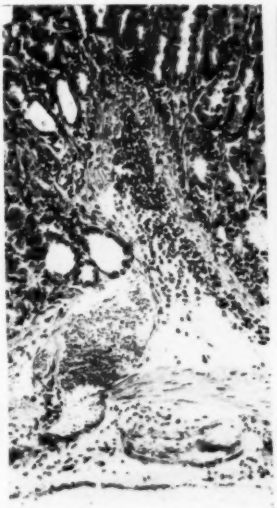

FIGURE 4.—Wall of stomach of strain I mouse with glandular mucosa above and musculature wall below. To the left of the center a group of glands has penetrated the muscularis mucosa and appears to be indenting the wall of a vein in the submucosa. Photomicro × 100.

FIGURE 5.—Wall of stomach of strain I mouse. A large vessel in the submucosa contains a glandular fragment from the mucosa. Photomicro × 100.

out gradually toward the pyloric sphincter. The squamous epithelium of the forestomach showed little change aside from hyperkeratosis in some of the older mice. The thickened areas in the glandular mucous membrane of the pyloric chamber were composed of polypoid glandular elevations representing originally modified rugae supported on connective tissue stalks and separated by deep crypts. Many individual acini were distended. On section, these dilated acini were round, oval, and elongated, with their long axes running in various directions (fig. 2). In some specimens there were microcysts with papillae and hyperplastic tubular glands that traversed a tortuous course toward the surface. The lining cells of these glands were often piled up two or more layers thick in alternating areas, imparting a saw-toothed appearance. The lining cells differed considerably in size, shape, and staining. Many cells were columnar, others cuboidal or polygonal, and some squamous.

The acini were usually empty, but a few contained stringy mucin, desquamated cells, and material resembling keratin. The stroma, which was congested and generally sparse, and fine, contained inflammatory cells, chiefly leukocytes. No metastases were found. Some of the dilated, atypical acini were found beneath the basement membrane—in a few instances in the muscular wall, rarely immediately underneath the serosa (fig. 3), and in two cases, there was a small mass of atypical, glandular mucuous membrane within a thin-walled vessel in the submucosa (figs. 4 and 5).

Andervont (*7*) made a comparison of the stomachs obtained from male and female strain I mice from 2 to 6 months of age and found that the lesion under discussion appeared earlier in the male. By the fourth month hyperplasia had occurred in practically every male, while many females of the same age had essentially normally appearing stomachs. However, in animals 6 months of age, the lesion was obvious in virtually all the mice of both sexes but was more pronounced in males. The latter tendency was maintained almost consistently throughout all older ages. The reason the lesion appeared earlier and was more pronounced in males than in females is obscure. Routine autopsies performed in this laboratory during the past few years have revealed a somewhat similar gastric lesion in a few old mice belonging to other inbred strains as well as in stock or market mice, but these lesions were far less extensive than those occurring even in younger mice of strain I. The occurrence of adenomatous gastric hyperplasia in mice of other strains is of some significance, for it shows that the tendency at least is not limited to one strain of mouse and suggests that consistent inbreeding has produced in strain I a stock in which the tendency has become pronounced.

Andervont (*7*) also carried out a genetic study to determine whether the lesion in the stomachs of strain I mice is inherited in accordance with genetic principles. Strain I mice were mated to C57 Black animals to procure outcross mice for genetic study. Mice of the C57 Black strain were selected because the lesion had not been seen in any member of this strain under 1 year of age and because the females take excellent care of their young. Reciprocal crosses were made between strain I and strain C57 Black mice. The F_1 hybrid generations resulting from these matings were then backcrossed to their respective parent strains. Results of the F_1 hybrid-generation mice showed that none had a gastric lesion, nor was any lesion of the stomach observed in the offspring which resulted from the matings of the F_1 hybrid generation with the C57 Black mice. However, when the F_1 hybrid generation was mated back to the strain I animals, a number of the offspring developed the adenomatous hyperplastic lesion of the stomach. These studies indicated that the susceptibility to the development of the lesion is inherited as a recessive characteristic. Andervont expressed the opinion that a number of factors are involved in the inheritance of this lesion.

Further studies by Andervont (*8*) revealed that the lesion of the stomach in strain I mice is apparently not communicable, for it does not occur in mice of other strains when raised in close contact with strain I mice. It is not associated with the presence of any gross parasites, for histological studies of all stages in this development did not reveal the consistent presence of such organisms. Experiments were carried out to determine whether the gastric hyperplasia might be caused by any infective agents or might be due to a vitamin A deficiency. The stomachs of strain I mice which showed the adenomatous lesion in pronounced form were fed to mice of strain C. The strain C mice were then permitted to live for 6 months longer. When they were killed, all had normal stomachs indicating that if the lesion is the result of an infection the etiologic agent is specific for mice of strain I. Feeding affected tissues to young strain I mice did not hasten its appearance or increase the degree of its development in young animals. The lesions did not regress in older strain I mice fed a vitamin A rich diet and occurred in young strain I mice fed a diet rich in vitamin A. It may be concluded,

therefore, that the lesion is not the result of vitamin A deficiency. The lesion was more pronounced in young strain I mice kept on a dog-chow diet which contained roughage than in those fed diets which were either rich or deficient in vitamin A but which contained very little roughage. This suggests that the physical state of the diet may exert some influence upon the development of the lesion.

Injection of Carcinogenic Hydrocarbons into Wall of Stomach

Thirty male strain A mice, 3 months of age, received an injection of 0.03 to 0.05 cc. of a solution containing 10 mg. of methylcholanthrene per cubic centimeter of liquid petrolatum into the wall of the forestomach and pyloric chamber (Stewart (*2*)). Eight of the thirty mice developed tumors of the stomach, four of the tumors being papillomas, and four squamous-cell carcinomas, all involving the forestomach. The mice with tumors died at an average period of 14 months after injection.

Two of the papillomas measured 4 mm. and 6 mm. in diameter, and the other two were smaller. The larger lesions projected into the lumen of the cardiac chamber of the stomach. Structurally, each tumor consisted of a central stalk of connective tissue covered with squamous epithelium. The stalk was tall and narrow in three cases. In the case of the fourth lesion, a flat papilloma, the surface was studded with spinelike projecting papillae. The covering cells were fairly regular, well-differentiated, stratified squamous epithelium. Mitotic figures were numerous in one case. The epithelial covering of the tumor merged abruptly with the mucous membrane of the stomach on either side of the lesion without any marked hyperplasia of the cells at the zone of transition. The stroma of the tumor consisted of adult fibroblasts with a few well-formed blood vessels. In one case there were numerous infiltrating inflammatory cells. The smooth line of demarcation between the epithelium and the underlying stroma was not always maintained. On the contrary, there was a tendency in all specimens for masses and strands of squamous cells to penetrate, in limited numbers, the underlying stroma and become apparently separated from the surface cells. In three cases this cellular infiltration did not go beyond the basement membrane of the gastric mucosa. In one case there was a small epithelial lined cyst in the submucosa adjacent to the muscular wall of the stomach.

The four carcinomatous lesions of the stomach all lay within the forestomach and measured from 5 to 9 mm. in diameter. On section, each appeared as a round gray nodule elevated about 5 mm. above the surface level of the mucous membrane of the cardiac chamber. All but one of the lesions involved the anterior wall of the viscus. Three lesions had finely granular surfaces. The fourth was a craterlike ulcer covered with clotted blood, and the lumen of the viscus was filled with blood (fig. 6). In two cases there was a rounded, umbilicated, neoplastic lesion on the peritoneal surface. The surrounding gastric wall was puckered and retracted on all sides toward the peritoneal extension of the tumor. In one case, a portion of the liver adherent to the serosa of the stomach opposite the tumor contained a small abscess. Microscopically, the malignant tumors were papillary squamous-cell carcinomas showing extensive keratinization of the covering epithelium. The gastric mucous membrane at the junction with the lesion was hyperplastic and hyperkeratotic. One tumor was ulcerated, with the base of the ulcer situated at the level of the circular musculature. The lumen in this case was filled with blood. Every lesion exhibited frank infiltration of tumor

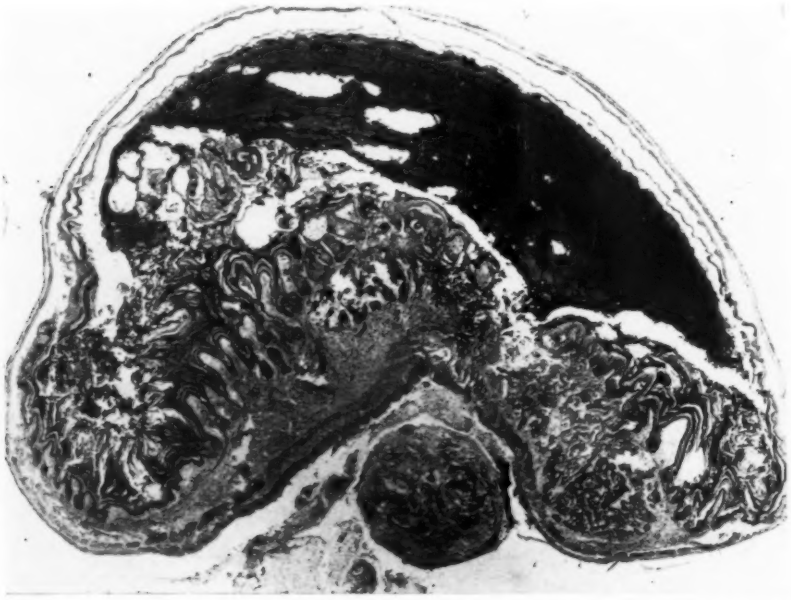

FIGURE 6.—Forestomach of mouse receiving an injection of a mineral-oil solution of methylcholanthrene into the gastric wall. There is an ulcerated squamous-cell carcinoma which forms a round nodule on the serosa outside the wall of the stomach. The lumen of the stomach is filled with blood. Photomicro × 10.

cells into the muscular wall of the stomach. The infiltrating epithelium was composed of basal cells, prickle cells, and flat squamous cells which were atypical in size, shape, and staining and showed numerous mitotic figures. The centers of the cellular masses frequently contained concentric layers of keratin, but in one tumor some of them were empty, suggesting an acinar structure with a squamous lining. In one case there were nests of epithelium within thin-walled channels, either lymph or blood vessels, situated between the two muscular layers of the gastric wall. The stroma of each tumor was infiltrated with inflammatory cells which were especially numerous along the course of the permeating tumor cells. In the case with the hepatic abscess, masses of keratin were in the center of the cavity. In two cases small nodules composed of tumor cells were adherent to the external surface of the peritoneum.

In one case bits of tissue from the squamous-cell carcinoma of the stomach were successfully transplanted for two generations when the transplantation was stopped. The morphology of the transplants was identical with that of the original tumor of the stomach.

ORAL ADMINISTRATION OF CARCINOGENIC HYDROCARBONS

Recently Lorenz and Stewart (*9*) described experiments in which squamous-cell carcinoma and other lesions of the forestomach were induced in mice following oral administration of aqueous mineral-oil or aqueous olive-oil emulsions containing either 20-methylcholanthrene or 1,2,5,6-

dibenzanthracene. To some of the emulsions 0.5 percent of the dioctyl ester of sulfosuccinic acid (trade name, Aerosol OT) was added for stabilizing purposes. The experiments were carried out as follows: Mice of strains A, C57 Brown, C57 Black, and C_3H were given orally an aqueous olive-oil emulsion of either methylcholanthrene or dibenzanthracene. Mice of strain A backcross were given the same olive-oil emulsion to which 0.5 percent of the dioctyl ester of sulfosuccinic acid was added. The third experiment consisted in administering orally to strain A backcross mice an aqueous mineral-oil emulsion containing either methylcholanthrene or dibenzanthracene. These experiments have been in progress now for 7 months, and the daily intake of emulsion has been approximately the same as that reported in previous experiments (Lorenz and Stewart (*10*)) along the same line.

In the mice which have come to autopsy up to the present time, there have been observed the following lesions of the forestomach in 40 animals: hyperkeratosis and hyperplasia of the mucosa, 6 instances; single or multiple papillomas, 24; and squamous-cell carcinoma, 10. In several animals all possible combinations of these lesions were present. In addition, 13 of the animals with changes in the stomach showed adenocarcinoma of the small intestine. The gastric lesions occurred earliest, in greatest proportion, and were largest in the mice ingesting the methylcholanthrene emulsions, and especially that prepared with mineral oil. All the gastric carcinomas to date have occurred in the strain A mice and strain A backcross mice ingesting methylcholanthrene emulsions.

The mice with hyperplasia and hyperkeratosis of the mucosa of the forestomach exhibited the lesion either in localized areas or diffusely. Microscopically, the change consisted of thickening of the squamous epithelium with a large amount of keratin on the surface and sometimes fibrosis and hyalinization of the submucosa.

The single or multiple papillomas observed in the forestomach were filamentous, sessile, or cauliflower in type. All

FIGURE 7.—Stomach of mouse receiving a methylcholanthrene-oil emulsion by oral administration. The forestomach is to the right, and the pyloric chamber to the left. The forestomach contains a large cancer along the line of the incision, and numerous discrete and confluent papillomas in the depth of the stomach. Photograph of gross specimen. × 4.

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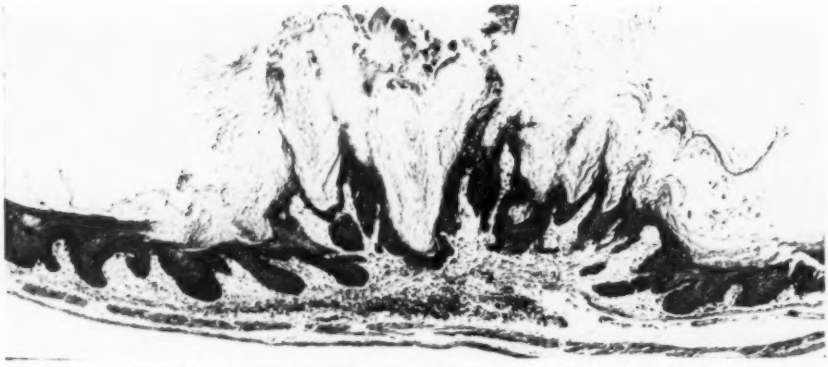

FIGURE 8.—Squamous papilloma of forestomach. Photomicro × 42.

these were confined to the cardiac chamber and were so numerous in some instances that practically the entire mucous membrane was involved. Microscopically, they consisted of a central core of connective tissue, containing blood vessels, and covered with hyperplastic and hyperkeratotic squamous epithelium. In some papillomas there were changes suggestive of early malignancy.

The majority of the stomachs with squamous-cell carcinoma were greatly enlarged, and a palpable mass could be outlined during life in the region of the stomach. The forestomach was enlarged several times, and the pyloric chamber was small. On the serosal surface, there were usually one or several nodules of varying size. In some cases, these carcinomatous nodules extended directly into the spleen, diaphragm, pancreas, and body wall. In several cases, there were grayish masses in the mesenteric lymph nodes, and in one case each a small gray nodule in the genital omentum and in the lung. Upon opening the stomach after fixation, the wall of the forestomach was found to be markedly thickened, either diffusely or in localized areas, by a grayish-white tissue which in many almost completely obliterated the lumen (figs. 7, 8, and 9). The mucosa of the pyloric chamber was not

FIGURE 9.—Squamous-cell carcinoma of forestomach with ulceration. Photomicro × 18.

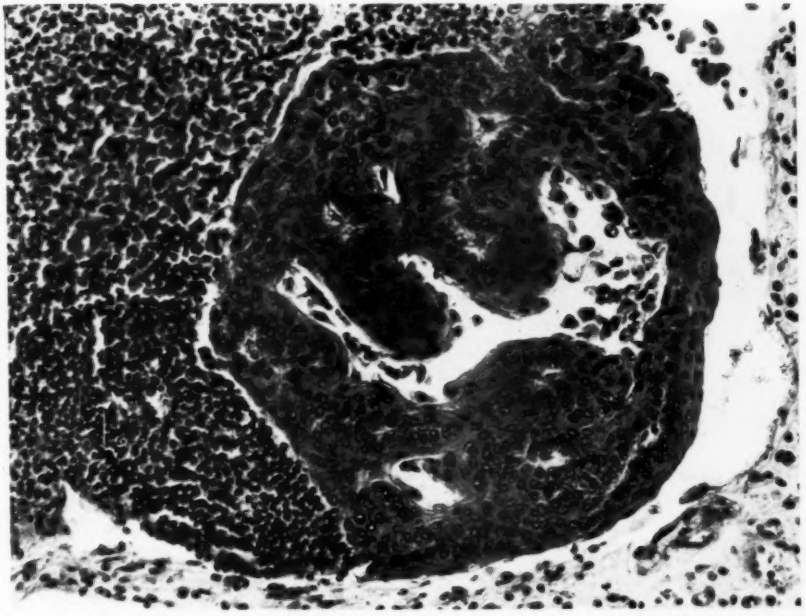

FIGURE 10.—Metastatic squamous-cell carcinoma of forestomach in mesenteric lymph node. × 235.

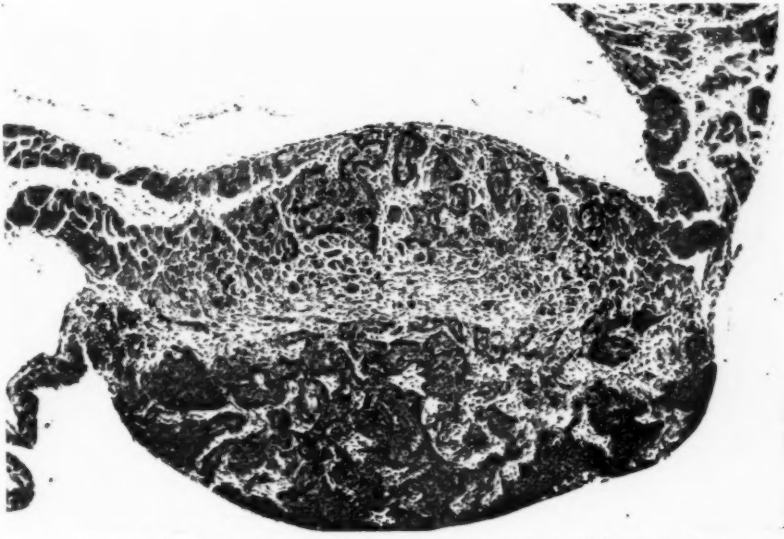

FIGURE 11.—Area of metastatic squamous-cell carcinoma of forestomach in diaphragm. Photomicro × 73.

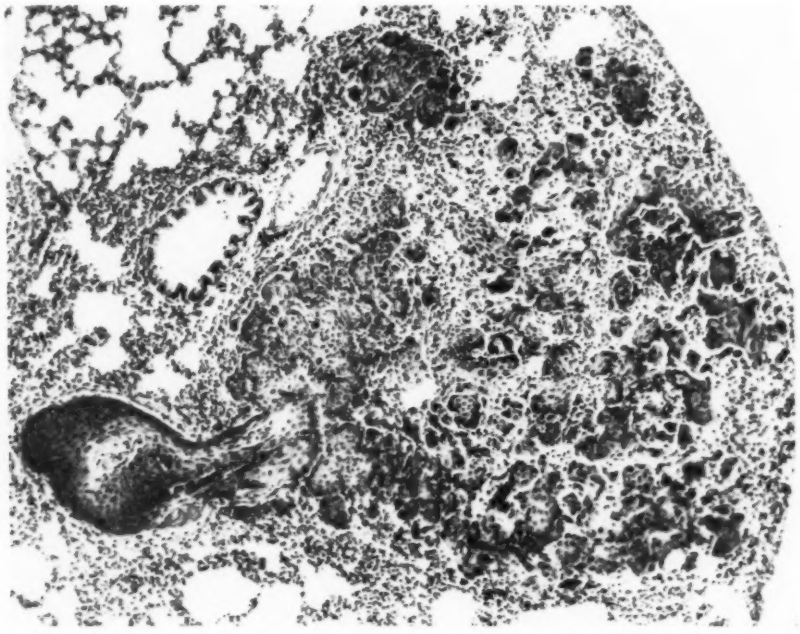

FIGURE 12.—Area of metastatic squamous-cell carcinoma of forestomach in lung. Photomicro × 105.

involved except in certain cases in which the cardiac mass overhung somewhat the glandular mucosa. Microscopically, all the carcinomas were of the squamous-cell type and showed extensive keratinization. The tumor tissue extended through all coats of the gastric wall, formed nodular masses on the peritoneal surface, and in three cases showed infiltration of, or metastases to the mesentery, pancreas, mesentery lymph nodes (fig. 10), genital omentum, spleen, diaphragm (fig. 11), chest wall, posterior abdominal wall, spleen and lung (fig. 12).

The strains of mice used in these experiments have not shown spontaneous squamous-cell carcinoma of the stomach in any instance in this laboratory.

DISCUSSION

There are in the literature relatively few claims to the production of experimental adenocarcinoma of the stomach. According to Klein and Palmer (*3*), these reports either are not convincing or do not permit objective evaluation of the malignant nature of the changes. There is no well-established case of adenocarcinoma of the stomach resulting from an experimental procedure.

The adenomatous lesion of the stomach in strain I mice is not considered to be malignant. The true nature of the gastric process, however, is not clear, although histologically it has been classified as an adenomatous overgrowth of the glandular mucosa. Somewhat suggestive of malignant growth in this lesion was the replacement of the gastric glandular mucosa by a complex arrangement of glandlike structures composed of altered epithelium with infiltration of atypical acini into the deeper part of the wall, and in two cases by permeation of veins. Although in

clinical material such findings are considered highly suggestive of malignant change, it would be unjustifiable to make the same interpretation in the case of the mouse. First of all, the deep extensions of the glandular fragments into the gastric wall were well limited and not disorderly as in cancer, and there was frequently a suggestion of contact between the surface mucosa and the more deeply placed fragments through a fold in the wall of the stomach. Although large irregular acini indented the basement membrane in many places, only one or two atypical fragments gained access to the deeper tissues in any specimen. The glandular mucosa was roughened and wrinkled but freely movable on the underlying muscle. In the next place, metastases have not been observed in any of our material obtained from strain I mice. A few adenomatous tumors were found in the lungs of some mice; but since these corresponded in all respects to the common pulmonary tumor that is characteristic of this species, there is no reason for regarding them as embolic deposits from the stomach. As further attesting to their nonmetastatic nature, these pulmonary growths appeared in increasing numbers following subcutaneous injection into strain I mice of 1, 2, 5, 6-dibenzanthracene corresponding in this respect to the pulmonary tumors of strain A and other mice.

The gastric process in the strain I mice develops remarkably symmetrically, all specimens with lesions conforming to the same general pattern. Instead of a single tumor arising in a different portion of the stomach in various specimens, the lesion reduplicates itself from mouse to mouse with marked exactness, as may be observed when sections are obtained in the same plane in any series of cases. In the stomachs it is the same areas of all the animals that undergo the adenomatous proliferation. A dense, resistant mass forms along the immediate line of origin of the glandular mucosa and diminishes in extent toward the duodenal orifice making the pyloric chamber thick and rigid. Locally there is a suggestive resemblance to leather-bottle stomach, and the secondary physiological effects on the organism may be much the same. However, in contrast to the leather-bottle stomach of man, the adenomatous change in the strain I mice is superficial and chiefly limited to the mucosa.

Finally, it should be pointed out that the adenomatous lesion in the stomachs of strain I mice bears some analogy to a rare gastric condition occurring in man which has been reported under various titles, such as, "gastritis polyposa," "adenomatosis gastrica," and "adenopapillomatosis gastrica." The pathologic picture is well described by these terms, and those who have had personal experience with the disease consider that it may originate in either of two ways: (1) As congenital hypertrophy of the epithelium; or (2) as hyperplasia acquired through chronic inflammation. One writer claims to have demonstrated all stages from hypertrophic gastritis to adenomatous formation and even to carcinomatous change (Konjetzny (*11*)). There is evidence that a congenital factor may be present. In human beings the disease has been found in twins, brothers and sisters, and in mother and son. In 7 percent of a series of cases collected by Brunn and Pearl (*12*), it was associated with generalized polyposis of the intestinal tract, a condition which shows a distinct familial tendency.

The criteria of induced malignancy of the stomach have been outlined by Klein and Palmer (*3*). According to these authors, proof of malignancy is not given by the histologic appearance of the tumor, whether spontaneous or induced, but by

the demonstration of malignant activity as evidenced by (1) the ability of the growth to proliferate independently as metastases, (2) the ability to invade progressively and destructively neighboring tissues and organs, (3) irreversibility of these activities which must be shown to continue in the absence of the extrinsic factor initially held responsible for the cellular changes. It must, furthermore be shown that a given malignant change occurs with sufficient regularity to establish a causal relationship of the experimental procedure to cancer. In the case of the squamous-cell carcinomas of the stomach which have been produced in mice both by injection of carcinogenic hydrocarbons into the wall of the stomach and by oral administration of these substances, these criteria of malignancy have been fulfilled. The largest gastric tumors obtained are those that have resulted from the oral administration of the carcinogen. These large tumors extend through the wall of the stomach infiltrating surrounding tissues and organs such as liver, spleen, pancreas, mesentery, diaphragm, and body wall, and they metastasize to the mesenteric lymph nodes, genital omentum, and lung. All these tumors have arisen from the squamous epithelium of the forestomach. No tumor of the glandular portion of the stomach has been induced despite the long-continued oral administration of potent carcinogenic hydrocarbons in high dosage.

The latest experiments of Lorenz and Stewart (*9*) illustrate that the induction of squamous-cell carcinoma of the forestomach of mice depends in part upon the selection of the medium in which the carcinogenic hydrocarbon is administered and in part upon the strain of mouse used. In this respect, the use of mineral oil in preparing the emulsion containing the hydrocarbon is much more effective in inducing gastric carcinoma in mice than are emulsions prepared with olive oil.

It is generally accepted that squamous-cell carcinoma of the forestomach has been experimentally produced in rats and mice by other investigators. However, as pointed out by Klein and Palmer (*3*), the impression given at times that it has been produced rather commonly is not supported by a review of the literature. The actual number of instances on record is difficult to estimate in view of the doubtful malignancy of some induced lesions of the forestomach regarded as carcinomas and the questionable relation of some of these to the experimental procedure. Klein and Palmer expressed the opinion that up until the time of the first publication of their paper (June 1940), there was no photomicrograph in the literature of a so-called metastasis to the lung from a squamous-cell tumor of the forestomach that cannot be matched among those of spontaneous pulmonary lesions, illustrated in the papers of Passey, Leese, and Knox (*13, 14*). As regards the metastatic lesion which we have shown from the squamous-cell carcinoma of the stomach in a mouse fed an emulsion containing a carcinogenic hydrocarbon, the appearance of this metastatic pulmonary tumor is entirely different from the spontaneously developing squamous lesions of the lungs. This lesion consisted of a wedge-shaped mass, the base toward the pleura, of proliferating squamous epithelium in the alveoli and alveolar walls, and the presence of a mass of squamous epithelium in a large blood vessel leading to this area, thus indicating an embolic type of metastasis.

Transplantation of squamous-cell tumors of the forestomach usually has not been attended by success. This may have been due to (1) infection of the implant, (2) the nonmalignant nature of some of the tumors, (3) the large amount of acellular

and keratinized material present, or (4) the difficulties in transplanting tissue from one strain of animal to another. Fibiger (*15*) apparently succeeded in the case of 1 mouse. Metastatic lesions of lymph nodes were transplanted successfully into 28 of 55 mice by this author and the transplanted tissue maintained the histologic appearance of the original tumor covering 4 generations of takes for a period of 1 year. Slye, Holmes, and Wells (*5*), in the case of 2 spontaneous gastric carcinomas in mice, obtained only a few successful transplants with 1 of the tumors which could not be carried to a second generation. We have succeeded in transplanting an induced squamous-cell carcinoma through 2 generations, the transplants being identical in structure with the original tumor.

From the morphologic description of the lesions obtained in this experiment, it is apparent that the division of tumors into papilloma and carcinoma was an arbitrary one for the purpose of classification. This division was made on the basis of the presence or absence of invasion of the deep muscular coats of the stomach by tumor cells. Such invasion was present in the lesions diagnosed as carcinoma, and it was absent in the specimens of papilloma. However, in the specimens of papilloma, the smooth line of demarcation between the surface epithelium and the underlying stroma was not always maintained. Instead, most of these specimens exhibited to some extent excessive growth of epithelium with extension of tumor cells through this barrier into the underlying stroma in the form of masses and strands of cells apparently detached from the surface epithelium. In one case there was a mass of atypical epithelium below the basement membrane in the submucosa. These findings suggest that under the conditions of the experiment, of injection of carcinogenic hydrocarbons into the wall of the stomach, transition stages may occur between papilloma of the stomach and carcinoma similar to the development of squamous-cell epithelioma from apparently benign papillomas of the skin on an area of the epidermis subjected to applications of a carcinogenic agent.

Of the attempts to produce experimental tumors of the stomach by injection of a carcinogenic agent into the wall of the stomach as reviewed in the introduction to a previous paper (Stewart (*2*)), there are two which have a bearing on the present experiments. Ilfeld (*16*) inserted pellets of benzpyrene under the gastric mucosa of six ferrets and 1,2,5,-6-dibenzanthracene pellets into the gastric wall of a dog with negative results after a year. Nothing is known at present regarding the latent period of induction of tumors in the ferret, but a recent study by Passey (*17*) has shown that in the dog it required several years to evoke tumors of the skin by painting with a carcinogenic tar. It seems, therefore, that the period of observation in Ilfeld's experiments might not have been long enough for positive results to be obtained. Uehlinger and Schürch (*18*) obtained sarcoma of the stomach in two of eight rabbits following implantation of a mixture of mesothorium in petrolatum into the wall of the stomach.

SUMMARY

Studies of an adenomatous, hyperplastic lesion of the glandular mucosa of the stomach of strain I mice are presented. The results of experiments on induction of squamous-cell papilloma and carcinoma of the forestomach in other strains of mice receiving injections of 20-methylcholanthrene into the wall of the stomach or aqueous olive-oil or mineral-oil emulsions of 20-methylcholanthrene or 1, 2, 5, 6-dibenzanthracene by oral administration are also presented.

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DISCUSSION

Chairman Voegtlin: Dr. Gardner was unable to be present on account of sickness, and Dr. Oughterson has consented to give briefly some results of Dr. Gardner's work which he has done up to date.

Dr. Gardner (Read by Dr. Oughterson): Before commenting on Dr. Stewart's paper, I should like to present certain data available from our laboratory. During the past several years the occurrence of malignant epithelial tumors of the uterine cervix in mice receiving injections of estrogens has been demonstrated in several laboratories. Such tumors are extremely rarely observed in untreated animals.

The question arose as to whether or not the intravaginal instillation of benzpyrene and methylcholanthrene would induce epithelial tumors of the vagina or uterine cervix. Would these tumors resemble those appearing in the estrogen-treated mice?

Sixty-one mice of 5 inbred strains and 2 groups of hybrids (15 mice) received intravaginally twice weekly 0.03 cc. of benzpyrene or methylcholanthrene dissolved in sesame oil (10 mg. per 1 cc.). Mice of the A and C57 strains also received 1 microgram of estradiol benzoate with each injection. The other groups were ovariectomized. All mice were from

39 to 136 days of age when treatment was started. They were kept in wooden boxes. Food (Purina Fox Chow) and water were available at all times. The oily solution of carcinogen was injected into the upper vagina through a blunted 22-gauge hypodermic needle. The mice were held so that the vagina was open and usually held the entire injection readily. After releasing the mice a part of the injected material usually escaped.

The observations pertinent to the present discussion are summarized briefly (table 1). Two points of lesser interest are also indicated: (1) The incidence of papillomas and more commonly carcinomas of the skin of the external genitalia and perineum indicates the susceptibility of skin to these substances; and (2) the incidence of tumors of the vagina or lower cervix was extremely low although the chemical was initially applied at these points. It would seem that the vaginal epithelium had a strikingly different sensitivity than the skin.

Of greater interest is the incidence of gastric lesions. These appeared entirely in the latter group. Of the 23 mice, 8 have shown gastric lesions which have been considered malignant, and 2 have shown small papillomas. All of the mice were of the C_3H strain. The tumors appeared after 198 to 321 days of treatment. As Dr. Stewart showed in his earlier papers, most of these lesions were largely confined to the upper stomach, although grossly the lower part of the stomach was also involved in several animals. This involvement was always by extension from the cornified upper stomach. Several animals showed enlargement of the lymph nodes in the upper mesenteries, but metastatic growth were not observed.

The lesions varied considerably in microscopic structure, as has been reviewed by Dr. Stewart. All of them consisted of squamous cells showing variable tendencies to undergo keratinization. The muscular layers of the stomach were always invaded, and frequently masses of epithelial cells were found growing in the serosa. The papillomas were likewise comparable with similar lesions described by Dr. Stewart.

The vagina was free from evidences of neoplasia, whereas the surrounding skin was usually involved with large ulcerating tumors. The intravaginal application did not prevent the spread of the material to the surrounding tissue. Likewise, even brief observation indicated that the oil solution was frequently licked from the skin around the vaginal orifice. The gastric tumors apparently can be well

TABLE 1.—*Distribution of tumors in mice receiving 0.6 mg. of carcinogen intravaginally in two injections weekly for long periods*

Strain	Number of ot mice	Duration of treatment	Treatment	Location of tumors		
				Perineum	Uterine cervix	Stomach
		Days		*Number*	*Number*	*Number*
A	4	182–310	M [1] and E [2]	3	0	0
C57	7	197–314	M [1] and E [2]	5	0	0
CBAN	3	119–271	BP [3]	0	0	0
Hybrids	9	147–329	BP [3]	5	0	0
CHI	12	125–332	M [1]	6	1	0
Hybrids	6	166–282	M [1]	5	1	0
C_3H	35 total, 12 alive	198–321	BP [3]	21		2 papillomas, 8 carcinomas

[1] M=methylcholanthrene.
[2] E=estradiol benzoate 1 microgram twice weekly.
[3] BP=benzpyrene.

explained on the basis of the oral intake of the carcinogen.

The observations from our laboratory considered by themselves indicate that the strain of mouse used might greatly alter the response. All of the gastric tumors were found among mice of the C_3H strain. Also these mice had all been ovariectomized. On the other hand, ovariectomized mice from other strains did not show gastric lesions.

The incidence of gastric tumors in non-carcinogen-treated mice in our laboratory is extremely low. But three have been observed in the mice examined. One of these was in a male from the A strain—exact age unknown, but over 500 days. The other two were observed in two male C_3H mice, 631 and 618 days of age, which had received weekly subcutaneous injections of stilbestrol plus triphenylethylene and estradiol benzoate plus triphenylethylene. These tumors were much like those appearing in the mice receiving the carcinogen, benzpyrene, especially those in which keratinization was most extensive. The incidence of such tumors would be very low in mice of these strains if based on the number of mice examined at death, and approximately 1 percent if only mice living to 600 days are considered.

Attempts were not made to transplant the gastric tumors.

Dr. Oughterson: May I make one comment? It is well known that adenocarcinoma of the stomach in the experimental animal is extremely rare. Beginning with the work of Fibiger, no matter what method was used—whether it was cockroaches, or dietary methods, or burrs placed in the stomach, or chemicals—adenocarcinoma did not result in the stomach. Squamous-cell carcinoma of the fore part of the stomach is the characteristic lesion, whereas in man adenocarcinoma is the common type of cancer. Why is it so difficult to produce adenocarcinoma of the gland-bearing portion of the stomach in the experimental animal? We have also heard some evidence today that human carcinoma is preceded by changes in the stomach which are manifested by changes in the hydrochloric acid and other changes in the secretions of which we know much less. Evidence, presented in England, shows that the relatives of patients with cancer of the stomach traced through some generations show abnormally high incidence of low acids. Evidence, shown at the Mayo Clinic, indicates that people with abnormally low acids show an abnormally high incidence of cancer of the stomach. There is now evidence that cancer of the stomach in man is preceded by some form of chronic gastritis. I would make the suggestion that possibly there is some protective mechanism present in the mice as normally found which prevents this portion of the stomach from being affected by the chemical carcinogens. In order to obtain experimental adenocarcinoma of the stomach it may be necessary to destroy this protective mechanism.

Chairman Voegtlin: Dr. Lorenz will discuss Dr. Stewart's paper.

Dr. Lorenz: For the past 3 years I have been studying the mechanism of tumor production by certain carcinogenic hydrocarbons. In the course of these experiments the question arose what the fate of the hydrocarbon would be when orally administered. A brief resume of this work will clarify certain aspects of the experiments on the production of tumors of the stomach in mice.

1,2,5,6-Dibenzanthracene was the first of the hydrocarbons to be tried. It was administered in the drinking fluid rather than mixed with the food. As drinking fluid an aqueous olive-oil emulsion was used, the 1,2,5,6-dibenzanthracene being

dissolved in the olive oil before emulsification. Strain A backcross mice were used as experimental animals.

This emulsion was toxic to the animals, and great care had to be taken to keep the mice alive for sufficiently long periods. It was finally possible to maintain them on this regime for a period as long as 9 months in one experiment and as long as 13 months in another. Details of these experiments are given in a paper published in the first issue of the Journal of the National Cancer Institute. The fate of the hydrocarbon was studied by analyzing the ether extracts of the gastrointestinal tract and other organs and tissues by the absorption spectrum method. It was found that 1,2,5,6-dibenzanthracene was present unchanged in the gastrointestinal tract down to the ileocecal junction. In the large intestine a new band system appeared, indicating a conversion product of the hydrocarbon. Within the limits of the sensitivity of the method, no spectrographic evidence of 1,2,5,6-dibenzanthracene was found in the organs outside the gastrointestinal tract.

No tumors of the gastrointestinal tract were observed in the first two experiments, although the mice ingested up to 180 mg. of 1,2,5,6-dibenzanthracene. Systemic lesions, particularly atrophy of the genital and hematopoietic tissues, were observed. Furthermore, pulmonary tumors were induced, indicating the possibility that some of the hydrocarbon had been absorbed from the gastrointestinal tract.

At this time, two explanations of the failure to obtain tumors of the gastrointestinal tract were considered: (1) The gastrointestinal tract of strain A backcross mice might not have been susceptible to induction of tumors by this method; and (2) the technique of administration of the carcinogen might not have been ideal.

New experiments with strain A mice and strain A backcross mice were then started. Moreover, at this time it was decided to extend this study to the use of 20-methylcholanthrene. Therefore, an olive-oil emulsion of this hydrocarbon was also prepared. In this series of experiments, intestinal tumors were obtained after the ingestion of approximately 125 mg. of 1, 2, 5, 6-dibenzanthracene in the strain A mice and of 180 mg. of 20-methylcholanthrene in the strain A backcross animals. 20-Methylcholanthrene appeared to be less toxic than 1, 2, 5, 6-dibenzanthracene, and the strain A backcross mice tolerated the ingestion of doses up to 280 mg. of this hydrocarbon during a period of 10 months.

As indicated, the tumors in these experiments were localized in the small intestine, and no tumors above the pyloric ring were obtained. Evidently the emulsion was removed rapidly from the mouth and esophagus especially by intake of food and the contact of the carcinogen with this section of the gastrointestinal tract was only intermittent. As the emulsion is not stable at pH less than 7, oil globules are probably formed in the stomach which mix with the food, preventing to a certain degree intimate contact of the oil with the wall of the stomach. In the small intestine, however, the olive oil is digested. The hydrocarbon probably precipitates, and very fine particles coat the intestinal wall. Most of the tumors appeared about 15 cm. from the pylorus. This may indicate that this area of the small intestine is particularly susceptible to the induction of cancer, or that the maximum precipitation of the hydrocarbon occurs in this location.

The experiments were next extended to administering the olive-oil emulsions containing hydrocarbons to several strains of mice: C 57 Brown, C 57 Black, C_3H, and A. In addition, some olive-oil emulsions were stabilized by the addition of a wetting agent, the dioctyl ester of sodium sulfosuccinic acid, which prevents the breaking

of the emulsion after acidification. A mineral-oil emulsion, with the same wetting agent as emulsifier, was also prepared. The results obtained up to the present indicate that the original olive-oil emulsion containing methylcholanthrene induced papillomas, hyperkeratosis, and hyperplasia of the forestomach in C 57 Brown, C 57 Black, and C_3H mice. In strain A mice it produced in addition a few cases of squamous-cell carcinoma of the forestomach. The strain A backcross mice, which in the former experiment had ingested up to 280 mg. of 20-methylcholanthrene without showing any lesion of the stomach, developed several squamous-cell carcinomas of the forestomach besides the other stomach lesions when administered the stabilized olive-oil emulsion. With the mineral-oil emulsion containing 20-methylcholanthrene 10 squamous-cell carcinomas have been obtained up to the present in strain A backcross mice. The first tumor appeared after 3 months, during which time not more than 70 mg. of 20-methylcholanthrene were ingested.

The different emulsions containing 1, 2, 5, 6-dibenzanthracene have so far produced only papillomas, hyperkeratosis, and hyperplasia of the mucosa of the forestomach.

The following conclusions are drawn from these experiments: (1) Mice are susceptible to the induction of carcinoma of the forestomach by the oral administration of carcinogenic hydrocarbons. The most susceptible strain of mouse so far observed is strain A; (2) tumors of the forestomach can be produced more easily by the use of stabilized olive-oil emulsions and most readily by the use of mineral-oil emulsions containing 20-methylcholanthrene.

The mechanism of this action is unknown at the present time. It can be postulated, however, that the stabilized olive-oil emulsion and the mineral-oil emulsions coat the mucous surface of the forestomach with a layer of emulsion which adheres for an appreciable time. It is also possible that the mineral-oil emulsions, having a greater viscosity than the stabilized olive-oil emulsions, remain longer in the forestomach. Absorption spectrum analyses to be undertaken will elucidate this question.

Future experiments may decide whether tumors of the glandular portion of the stomach can be induced in mice. The squamous mucosa of the forestomach of mice may be so susceptible that squamous-cell carcinoma is induced relatively early and the animal dies before a lesion of the glandular portion has had time to develop. Certain strains of mice may be found in which the glandular portion of the stomach is more susceptible. If this is not possible, other species of animals, such as the guinea pig, may be tried. Different types of mineral-oil emulsions, and other variants in the physical state of the carcinogen, such as colloidal aqueous solutions, may produce this type of neoplasm. Experiments along this line have been started.

Dr. Shear: I should like to comment briefly on some related work now in progress. Although the adenomatous lesion in the stomach of strain I mice which Dr. Stewart has just described was not considered definitely malignant, it seemed to offer material for further work. In collaboration with Dr. Andervont, I fed to mice of the I strain diets containing azo dyes, which by oral administration to rats had been found by Japanese workers to produce tumors in the liver. Those experiments were started some years ago and have now been completed. The two dyes were 2-amino-5-azotoluene and *p*-dimethylaminoazobenzene. The gross findings showed no marked difference from those in the control mice. The histological material is now being examined, and it is not yet possible to say whether any of

these tumors have been made malignant by this procedure.

Another line that was gotten under way last year involved the use of dogs. For a number of years, in discussions with Dr. Hollander, of New York, we felt that the dog might offer advantages over the mouse and the rat in studies of gastric carcinoma because the dog's stomach bears a greater resemblance to the human stomach. Some work has been started with Dr. Hollander and his associates, using the dog. The techniques are at present being worked out, and Dr. Hollander will have a few comments to make on that.

The last point I wish to make is that there are still other procedures which might be used in an attempt to provide material for the systematic investigation of stomach tumors, namely, the regular production of glandular carcinomas in the stomach of some experimental animal.

Dr. Hollander: I will try to be brief and simply tell you of several techniques which we have evolved and which are in process of improvement at the present time. In contemplating the work which has been reported on this afternoon by Dr. Stewart and Dr. Lorenz, Dr. Shear and I became aware of certain difficulties inherent in the use of the rodent for the production of experimental gastric tumors. For one thing, one cannot be sure how the application of a carcinogen is localized when it is administered by mouth. For another, one is not certain that mucus, which is secreted by the healthy stomach normally and is secreted in response to an irritant in even greater amounts, does not serve as a protective agent against the surface application of a carcinogen to the gastric mucosa. This phenomenon might very well account for the fact that a squamous-cell tumor is developed in the forestomach of the rodent, but no true adenocarcinoma is produced in the glandular stomach. Then, too, in envisioning this entire problem, one must plan to study progressive changes in gastric physiology and in morphology, both gross and minute. From the very first day that one starts applying a carcinogenic agent of any kind, one ought to be able to say that a response has or has not been elicited, without sacrificing the animal. It may be that there is an immediate response which evokes a protective action of some kind, as a result of which the carcinogenic agent is shed, and its immediate effects are offset. In consequence of this no tumor would be developed, although there had been an immediate reaction of significance for the purposes of the investigation. Above all, it is necessary that such studies be made without sacrificing the animal and that it be kept alive and generally healthy for years, if necessary.

These are some of the conditions which one must face in laying out a project for the study of experimental gastric cancer, as Dr. Shear and I saw in our early discussions on the subject. In order to meet these conditions, we felt, it was necessary to use a larger animal like the dog—which would offer an additional advantage in that such studies would be initiated with a species higher than the rodent—and to develop techniques specifically adapted to the requirements of our problem.

In an effort to develop such techniques with the assistance of Drs. Druckerman and Bandes, of my laboratory, we have already been successful to this extent. (Slide) The first method which we have developed has been based on the formation of a simple gastric fistula in the dog, which is closed by a sphincter. The surgical technique for the preparation of these fistulas was described in the literature years ago, and it is not new with us.

This is a close-up photograph of the mouth of one such fistula, taken some 4 or 5 months after the fistula was prepared. You observe that there is no sign of erosion around the mouth of the opening, although the animal receives no dressing whatsoever on the abdominal wall. The fistula is absolutely tight, and there is no loss of stomach contents. On the other hand, it is possible to put a suitable endoscopic instrument through that fistula for observation of the entire interior of the stomach, from the cardiac orifice right down to the pylorus. It is possible to apply solutions and ultraviolet irradiation to the surface of the mucosa, to take biopsies, and to take photographic records of the interior of the stomach if that should become necessary.

(Slide) The second technique which we have developed depends on the preparation of an exteriorized flap of gastric wall; a small part of the stomach wall, including the seromuscular layer with blood supply attached, is brought out and sutured to the outer abdominal wall of the animal. This is a close-up color picture of one of these flaps taken 3 weeks after the operation. The original midline incision is still visible. This particular flap is about 20 x 40 mm. in size. Some flaps prepared subsequently are two to three times this size. By and large they are normal, so far as one can tell grossly at this time. Three of the four such animals that we now have continue to secrete acid from their flaps, even several months after preparation; the fourth one never did. Here again, it is possible to apply a carcinogen directly to the surface of the mucosa or to inject it intramucosally; it is possible by suitable chemical treatment to evoke a preliminary flow of mucus, wipe it away, and then apply the carcinogen; it is possible to apply ultraviolet irradiation to a flap of this kind, either alone or in conjunction with chemical agents, and to study the effects which may develop as a result of these several treatments

(Slide) This is a photograph of a dog, showing a special metal guard which we have developed for the protection of these flaps. The cap on the guard can be removed easily, and the agent applied to the mucosa or studies made of the tissue without removing the dog's jacket.

In addition to applying chemical carcinogens directly to the surface of the mucosa, we have been studying the possibility of injecting solutions of these substances into the mucosal layer. (Slide) This is a section of the gastric wall of a dog, into which we have injected india ink suspended in saline. I show it to you in order to demonstrate that one can effect a dispersion of an oily solution of benzpyrene, for instance, throughout the glandular structure without bringing it in contact, at the outset at least, with the seromuscular layer. We consider this rather an important point of technique in an effort to develop an adenocarcinoma rather than a sarcoma.

We are still concerned with making minor improvements in these techniques, but preliminary studies by means of them have already been started. These studies include observations on mucus and acid secretion and gastritic changes in the tissue, in response to various irritants, including carcinogens. Actual attempts to produce gastric neoplasms, Dr. Shear and I feel, must remain secondary to more fundamental studies like these, for some time to come.

Chairman Voegtlin: Dr. Stewart, will you close the discussion?

Dr. Stewart: I think this discussion has been interesting. I see no reason why we shouldn't hope ultimately to produce carcinoma of the glandular portion of the stomach. I think with perseverance, perhaps using different strains of animals,

perhaps different hydrocarbons, or, as Dr. Hollander has pointed out, different techniques, this lesion will ultimately be produced experimentally.

Chairman Voegtlin: This closes this afternoon's session. (The meeting adjourned at 4:20 p. m.)

SATURDAY MORNING SESSION

OCTOBER 12, 1940

(*The meeting convened at 9:35 a. m., Dr. Ludvig Hektoen, presiding.*)

Chairman Hektoen: The first paper this morning is by Dr. C. P. Rhoads, Director, Memorial Hospital, on Gastric Cancer as a Sequel to Gastritis, Particularly the Gastritis of Pernicious Anemia.

Gastric Cancer as a Sequel to Gastritis, Particularly the Gastritis of Pernicious Anemia

By C. P. RHOADS, *director, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York*

Any consideration of the possible etiology and control of the changes in gastric mucous membrane which lead to the development of cancer of the stomach must be, at the moment, largely literary and speculative. It does seem wise, however, at a time when an organized attack on the problem of gastric cancer is in the making, to review the available information and from it to develop a hypothesis which may be subjected to experimental test. For these reasons I have taken the liberty of considering, in a scientific communication, certain evidence which is now largely of historical interest. This interest, however, coupled with experiments based upon modern methods of precision, may well lead to investigations which otherwise would not be made.

It is commonly stated that the first communication concerning a derangement of gastric secretion associated with cancer of the stomach is that of Golding Bird (*1*) published in 1842. In this paper Bird draws "attention to the characters of the fluid ejected from the stomach in those cases of gastric affection in which no evidence of organic, or at least of disorganizing, affection existed * * *. The vomited fluids, when possessed of acidity at all, never contained any considerable quantity of free acid." The case described in this paper and supposed by many to have been one of carcinoma of the stomach, actually appears to have been that of a person showing free acid in the gastric juice and very likely was really a case of pyloric stenosis with ulcer. However that may be, the report stimulated other physicians to examine the gastric juice of patients with cancer of the stomach and, as all are now aware, free acid was found to be absent in a large proportion of the cases. The paper of Bloomfield (*2*) is a good example of this type of study. It presents the results of gastric analyses made upon a large number of normal iudividuals and compared with similar studies of patients with cancer of the stomach. The results show beyond question that gastric cancer very frequently is associated with achlorhydria and also with a diminished volume of gastric secretion, both facts which have since been abundantly confirmed in many clinics and are now generally accepted.

Two explanations of the achlorhydria have been advanced: (1) That the presence of the cancer interferes with secretion; and (2) that the neoplasm develops in a mucous membrane previously deranged, at least functionally. It is worthwhile to consider Bloomfield's contribution to this question. He states that acid never disappears progressively during the growth of gastric cancer, and so he agrees with the view held by Hurst (*3, 4*), that the tumor is prone to occur in stomachs already the seat of chronic changes. Bloomfield calls attention, moreover, to the well-known report by Hurst of the development of cancer of the stomach in a man previously known to have anacidity, a finding more recently confirmed on a larger scale by Comfort

(*5*). From this material, the evidence seems to be conclusive that gastric cancer is associated with gastric anacidity and is probably secondary to it in many instances.

The study by Usland (*6*) of the question of gastritis antedating the development of cancer provides further confirmation. Of 94 of his patients with such new growths, 26 had had gastric symptoms for over 5 years—conclusive evidence, he felt, that the tumor developed at the site of some chronic inflammatory or degenerative process. As a corollary to this study, 120 patients with chronic gastric symptoms were observed over an 8-year period, and of these 18 developed gastric cancer. Since carcinoma of the stomach is recognized to be a condition which progresses rather rapidly, it is difficult to believe that all of these individuals had fully developed cancer when their digestive symptoms first appeared. Hence it is possible that Usland's figures are valid evidence that gastritis does precede gastric cancer, in some instances at least.

It is next necessary to consider what anatomical change has interfered with secretion in these cases of gastric new growth, and particularly to establish whether the change is one which, on the basis of our knowledge of precancerous changes of other tissues, might conceivably lead to the development of neoplasm. The solution of this question was attempted by morphological studies of the gastric mucous membrane at sites well-removed from the neoplasm. A classic report on material of this sort is that of Orator (*7*). Twenty-five cases were studied; of these 15 showed a diffuse atrophic gastritis marked by loss of secreting glands and by an increase of connective tissue; 4 showed a hyperplastic mucous membrane with atrophic areas; 1 case showed only irregular gastritis of the fundus, with fairly serious involvement of the pylorus. The 5 remaining cases showed a normal fundus mucous membrane, and these were considered to be instances of gastric cancer developing as a sequel to ulcer.

The presence of associated gastritis has been abundantly confirmed, although few modern pathologists consider it to be as uniform a concomitant of gastric cancer as does Orator. An example of a confirmatory report is found in the publication of Konjetzny (*8*). On the basis of extensive pathological material, this author stated that the gastritis of cancer is regularly atrophic and quite generalized. He felt, furthermore, that he could trace the transition from the inflammatory mucous membrane to the neoplastic.

In spite of the apparent conclusiveness of these reports, a detailed review is required of histological material from stomachs which are the site of gastric cancer. Too frequently in the older studies fixation was poor, and the microscopical descriptions were incomplete. Dr. Stewart, of the Memorial Hospital, has a detailed study now in progress, and it is hoped that the results will be available in the near future. It seems fair to assume, however, that in certain instances gastritis is associated with cancer and, from the evidence previously discussed, that it precedes the neoplasm.

It is necessary next to consider the nature and cause of gastritis in general in the hope of establishing some common denominator which might lead to measures for controlling the precancerous type of lesion. Pernicious anemia affords an excellent example of gastritis unassociated with neoplasm, and it is of some interest to review our knowledge of this gastric disorder. The publication, in 1880, of a monograph by Fenwick (*9*) advanced irrefutable evidence that pernicious anemia is regularly associated with gastritis and presented convincing histological studies.

Indeed, very little can be added today to these beautiful clinico-pathological investigations. A considerable series of cases was studied, adequate fixation was observed, and the results are conclusive. Furthermore, sufficiently precise chemical tests were made to establish the regular association of achlorhydria with the morphological change of the mucous membrane.

Surprisingly enough, relatively few pathological studies were inspired by Fenwick's publication, although his conclusions were universally accepted as correct. This lack of confirmatory publications led Madeleine Brown (*10*), a few years ago, to restudy the autopsy material from the laboratory of Dr. Frank Mallory in the Boston City Hospital. Suitable specimens from 42 cases were obtained and examined. The results were striking. Chronic gastritis was regularly found, and the description of the lesion deserves quotation:

> The term is used to describe an interstitial infiltration of lymphocytes in the gastric mucosa. This infiltration was sometimes so marked that an actual hypertrophy of the mucosa ensued. * * * Often many of the glandular tubules had disappeared, and fibrous tissue had replaced them. Some of the glands had dilated into mucous cysts containing many goblet cells. A particularly striking feature was the absence of acidophilic cells, which were found in only 5 of the 42 specimens.

Not only did Dr. Brown's studies establish more firmly the association of gastritis with pernicious anemia, but they also called attention to an important new observation. She states, "The number of benign gastric tumors occurring in this series was the most unexpected finding of the study. The incidence in these 151 autopsies was 8 per cent, while among the 18,200 on patients dead with disorders other than pernicious anemia it was 0.003 per cent." The conclusion seems inevitable, not only that gastritis is regularly present in pernicious anemia, but also that it predisposes frequently to the development of polyps of the mucous membrane. This is most significant, since few would deny that polyposis is a precancerous condition.

The observations of Brown concerning polyposis appear to be confirmed by the impressions of most workers in hematology. Although there are relatively few published reports, gastric polyposis is certainly not an uncommon finding in pernicious anemia, and is quite uncommon in association with other disorders. Furthermore, it is not unreasonable to suppose that the persistence of an inflammatory process such as is clearly present in the gastric mucous membrane of the patient with pernicious anemia should lead to abnormal overgrowths of mucous membrane, exactly as persistent sinusitis leads to the formation of nasal polyps.

In view of the studies just mentioned, it is proper to inquire whether the incidence of gastric cancer is greater in patients with pernicious anemia than it is in patients with other disorders. One study pertinent to this consideration is that of Rambach (*11*). Of 11,849 patients autopsied, 641 had gastric cancer and 50 had pernicious anemia. In 11 instances, however, gastric cancer was associated with pernicious anemia, whereas the expected incidence of the association was only 2.4 cases.

An explanation of this coincidence frequently advanced is that the presence of gastric cancer interferes in some way with the production of the Castle principle formed in normal mucous membrane and required for normal blood formation. It is true that many instances of pernicious anemia following gastrectomy have been reported. It is not clear, however, why all cases of gastrectomy are not followed by pernicious anemia, nor why all cases of gastric cancer do not have a similar sequel if the

explanation of pernicious anemia is as simple as the removal of an hematopoietic secretion.

Another strong argument against the chance nature of the coexistence of gastric cancer and pernicious anemia is the fact that both diseases seem to appear in the

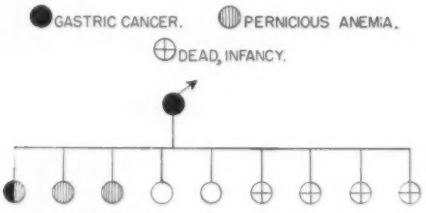

FIGURE 1.—Familial incidence of gastric cancer and pernicious anemia in five surviving children whose father died of gastric cancer. Chart made from data given by Borovanská (*12*).

same families. An example of this familial incidence has been published by Borovanská (*12*). Of five surviving children of a father dead with gastric cancer, two had no disease, two had pernicious anemia, and one had pernicious anemia with can-

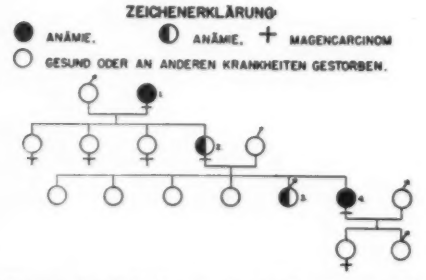

FIGURE 2.—Inheritance of anemia and anemia and gastric carcinoma in three generations. (From Thiele (*13*)).
●, Anemia; ◑, Anemia and gastric carcinoma; ○, Healthy, or dead from other diseases.

cer of the stomach (fig. 1). A similar observation was reported by Thiele (*13*) (fig. 2). Here again, these observations are confirmed by most hematologists, since the impression is widespread that gastric cancer is more frequently found in the family trees of patients with pernicious anemia than among the relatives of patients with other disorders, as shown by the publication of Zancan (*14*).

A further strong argument against the purely coincidental association of gastric cancer and pernicious anemia is found in the elaborate study of Cotti (*15*), and his conclusions deserve careful consideration. In 107 patients with neoplasms associated with pernicious anemia, 93, or 86 percent, of the tumors were located in the stomach. Confirmation of this general tendency of patients with pernicious anemia to die of cancer of the stomach rather than cancer of other organs is provided by Wilkinson's study (*16*), in which 70 percent of the tumors were gastric. Of all patients dying of malignant disease, something under 30 percent would be expected to die of gastric cancer. Cotti states that the association of pernicious anemia and cancer of the stomach cannot be regarded as exceptional; on the contrary the incidence is relatively high. He comes, furthermore, to another important conclusion when he states that the gastric tumors associated with pernicious anemia do not exhibit any characteristic gross or microscopic appearance. The forms most frequently encountered are the ulcerated and polypous ones, resembling in all features the carcinomas of other origins.

The final link in the chain of clinical evidence would be the demonstration that gastric cancer occurs more frequently in those who have had pernicious anemia which has responded to conventional dietary treatment than it does in normal individuals. If this sequence could be shown, a strong argument would be at hand for the precancerous nature of the gastritis of pernicious anemia. Unfortunately statistical proof probably is not possible. Table 1 presents 24 clear-cut

TABLE 1.—*Sequential occurrence of gastric cancer and gastritis of pernicious anemia as found in the literature*

Author	Case history of patient												
	When first seen					Treatment	After treatment					Time interval	Cancer confirmed by—
	Age	Red blood corpuscles in millions	White blood corpuscles per cu. mm.	Color index	Hemoglobin		Red blood corpuscles in millions	White blood corpuscles per cu. mm.	R [1]	Color index	Hemoglobin		
	Yrs.				*Pct.*						*Pct.*		
Thiele	59	1.4		1.25	35	Liver			R			5 yrs.	Surgery.
Cabot	60	1.0	4,000		25	do	2.3	7,000			60	(?)	Do.
Plummer	63	1.0		1.25	25	do	4.2			1.0	85	5 yrs.	Autopsy.
Roller	64					do						10 mos.	
Grill	46					As			R			3½ yrs.	Surgery.
Held	63	2.61		.9	50	Liver			R			8 yrs.	Do.
Conner	53	1.85	3,600	1.2	47	As	4.28				77	7–8 yrs.	X-ray.
Do	56	2.24	4,200	1.1	49	As and Fe			R			7½ yrs.	Autopsy.
Do	52	1.3	4,700	1.1	30	do			R			11½ yrs.	X-ray.
Meythaler	34	2.036	3,700	1.42	57	Liver			R			3 yrs.	Surgery.
Calabresi	59	1.7	4,000		43	do			R			2 yrs.	Autopsy.
Wilkinson	39	2.0	8,500	1.15	46	do	5.65	9,000		.97	110	5 yrs.	Do.
Silverman	57	1.575		1.1	36	do	4.19				74	5½ yrs.	Do.
Rambach	49	1.68	3,400	1.25	42	do	3.9	4,000		1.06	83	7 yrs.	Do.
Do	58	1.62	4,400	.93	30	do	4.28	11,350		1.0	86	5½ yrs.	Do.
Do	63	1.58	4,600	1.2	38	do	4.5				91	10 yrs.	Do.
Do	57	3.34	4,800	.99	66	do			R			1 yr.	Do.
Do	68					do			R			3 yrs.	Do.
Do	54	1.39	4,400	1.3	35	do	1.88				45	4 yrs.	X-ray.
Do	71	1.01		1.88	38	do	3.09				70	1 yr.	Autopsy.
Strandell	47	1.11	4,900	1.4	30	As	3.1	3,600		1.0	65	11 yrs.	Do.
Do	63	1.41	4,600		40	(?)	4.4	1,000			80	13 yrs.	Do.
Do	42	1.08	2,000		65	(?)			R			2–3 yrs.	Surgery.
Do	47	2.0	3,900	1.3	52	Liver	5.0	8,800		.8	80	5 mos.	Autopsy.

[1] R indicates recovery or improvement where blood count was not given.

instances, collected from the literature, of the sequential occurrence of the two disorders. Here again, a widespread impression exists that the sequence is more frequent than would be expected. In order to obtain unequivocal evidence concerning this point, it would be highly desirable to establish some sort of gastric cancer registry in which particular attention was paid to the hematological disorders which antedate the neoplasms.

For the sake of the argument, let us assume that the gastritis of pernicious anemia does predispose in some instances to malignant disease. On this supposition it is desirable to inquire into the etiology and reversibility of gastritis in the hope that some suggestion may be obtained of a way whereby the progressive course of the precancerous gastritis can be reversed.

Very probably the first *in vivo* evidence of transient inflammation of the gastric membrane was that obtained by Beaumont (*17*) in the course of his study of the stomach of Alexis St. Martin. The experiments are familiar to all of you, but it is of interest to review his observations. He stated, "St. Martin had been drinking ardent spirits pretty freely for eight or ten days past, and erythema and apthous patches began to appear." The lesions persisted for several days, but as the mucous membrane was observed it gradually returned again to a healthy appearance. This observation is one of great significance, since whereas gastritis is frequently thought of as a rare and often an irreversible process, for over 100 years evidence has been available to prove that it is common and is reversible at certain stages.

In view of these facts, the recent observation of Benedict and his coworkers

(*18*), which has aroused so much comment, is less unexpected. Previous to the development of the gastroscope, the gastritis of pernicious anemia was only seen at autopsy; and since the achlorhydria persisted, the idea was established that the gastritis persisted also. Hence when Benedict studied the gastric mucous membrane of five cases of pernicious anemia before and after successful treatment of the disease, his findings were remarkable. He stated, "Following specific therapy of the pernicious anemia, evidences of atrophy and hypertrophy of the stomach have both tended to disappear." He suggested, furthermore, that "the change * * * represents an epithelial change associated with successful treatment of a specific deficiency state, rather than the healing of a chronic inflammatory process."

The concept of Benedict is unique, and it is proper to examine the background of information which led to its development. The idea really dates back to the experimental production and cure by Goldberger (*19*) of the mucous membrane lesions of pellagra. The production was accomplished, as is well known, by feeding to prisoners deficient diets taken by individuals subject to the glossitis and intestinal disorders of pellagra. The cure was effected by supplementing the deficient diets with the lacking factor, of which yeast was found to be a rich source. When the group in Boston began to study pernicious anemia intensively in the period from 1920 to 1930, careful review of the evidence emphasized the general similarity of the symptoms of pernicious anemia with those of pellagra insofar as mucous membrane change, as well as neurological and gastrointestinal disturbances were concerned. Hence the ground was broken for the concept of pernicious anemia as a dietary disease. The first paragraph in the classic paper by Minot and Murphy (*20*) describing the cure of pernicious anemia by diet indicates clearly that the effect of diet on the disease had been known for many years, and it simply required the determination coupled with the precise methods of Minot to provide experimental confirmation.

Whereas the fact is well known that the stomatitis and the gastrointestinal manifestations of pernicious anemia disappear upon treatment with a dietary substance contained in liver and yeast, the idea that the gastritis behaves similarly had never been advanced until the publication of Benedict (*18*). Pernicious anemia was held to be a gastric disease, caused by some sort of hereditary failure of the function of the gastric mucous membrane. This resulted, it was supposed, in a failure of the mucous membrane to secrete the intrinsic factor described by Castle (*21*). Hence the gastric juice failed to convert a dietary constituent contained in yeast into a hematopoietic agent stored in the liver. No clear evidence has been advanced to refute this view, although it still embodies several unexplained features.

It is possible, however, that sprue, a clear-cut deficiency disease, may well give the answer to the etiology of gastritis. Hilary (*22*) was the first to describe clinical sprue, and his description is worth considering. He states: "The patient finds a burning heat in the oesophagus and stomach, attended by eructations and sometimes vomiting by which a clear, acrid lymph or watery phlegm, which is hot and most commonly very acid, is brought up, though in some few it is not so acid." This is one of the most significant presentations in medical literature. It describes the affection of all the intestinal mucous membranes which is so

prominent a feature of the disease. It indicates, furthermore, that whereas free acid is usually found in the gastric contents, in some achlorhydria is present.

The studies of patients with sprue by Castle (*23*) showed that some patients could be completely relieved by the administration of an extract of yeast which contained the dietary factor effective in curing pernicious anemia. In contrast to pernicious anemia, the dietary factor was effective without admixture with normal gastric juice. In other patients, however, the situation was analogous to pernicious anemia, and in these therapeutic effect was obtained only after the dietary factor was incubated with gastric juice. Extensive clinical studies suggested that a dietary lack was causative of the disease, and that in the early stages the disorder could be cured by administering the lacking factor. It appeared, however, that after repeated attacks some irreversible change of gastric mucous membrane took place. Clearly it was important to establish whether gastritis was present in the early stages of the disorder when it could be relieved by giving yeast. The presence of such gastritis is established by the studies of Rodriguez Olleros (*24*), which may be summarized as follows: In all the cases of sprue gastroscoped, some form of atrophic gastritis was seen, and, moreover, the lesions were found to be cured or greatly improved by dietary therapy "in much the same manner as has been found true of pernicious anemia."

From the available facts obtained in some 10 years' experience with tropical sprue, it is possible to present graphically our conception of the etiology of the mucous membrane change, gastritis, as well as inflammation of the oral, lingual, and intestinal mucosae. It appears that a diet low in its content of some substance associated with the vitamin B complex, possibly aided by the loss of chloride due to tropical climate and by infectious diarrhea with its attendant loss of absorptive power, leads to an acute reversible alteration of the gastric mucous membrane. This change can be cured by adding yeast or any other source of dietary hematopoietic factor to the food. If the deficiency is continued, however, some more profound change takes place, with a loss of the gastric anti-anemic factor. Here again, supplement of the diet with liver, meat, or yeast is therapeutically effective. If the deficiency is prolonged, some irreversible change takes place with complete loss of the gastric anti-anemic factor and some interference with absorption from the bowel. When this change has taken place, the disorder cannot be cured by the oral administration of the lacking factor, because of insufficient absorption, but it can be cured by its parenteral administration.

To summarize: It seems probable from the evidence that gastritis is associated with, and probably precedes the development of certain cases of gastric cancer. The association of pernicious anemia, in which gastritis is always present, with gastric cancer appears to be more frequent than could be explained by the laws of chance, and, furthermore, there is some evidence that if one disorder is present in a family the other is likely to occur. Gastric cancer as a sequel of pernicious anemia is not infrequent, and gastric polyposis is very much more common in pernicious anemia than in patients dead of other disorders. Modern gastroscopic studies indicate that the gastritis of pernicious anemia is in part reversible by the administration of a constituent of the diet. This observation is confirmed by experimental studies of sprue closely allied to pernicious anemia but clearly the result

of a dietary deficiency rather than of gastric dysfunction. Here again, the gastritis occurs when deficiency is marked and disappears when it is remedied.

The suggestion is advanced that certain forms of gastritis are in fact precancerous alterations, that they are the result of deficiency, and that they may be cured by adequate dietary supplement. It should be clearly understood that in no sense do we maintain that all gastric cancer, or even any large part of it, is the result of dietary deficiency, nor do we have any notion that the malignant change, once established, can be reversed by any dietary means. It is only hoped that these suggestions may lead to more serious consideration of dietary deficiency as a cause of precancerous gastritis, and to more serious efforts toward the dietary control of this disorder.

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DISCUSSION

Chairman Hektoen: The discussion of this paper will be opened by Dr. Schiff.

Dr. Schiff: Members of the Conference: I want to express my appreciation of Dr. Rhoads' excellent presentation of this subject. By way of discussion, I should like briefly to mention a few of our observations that have some bearing. These deal with (1) gastritis accompanying pernicious anemia, (2) gastritis associated with hypochromic anemia, (3) gastritis seen without either of these disturbances and in the absence of associated gastric disease, and (4) gastritis associated with gastric carcinoma. These observations are primarily clinical and gastroscopic in character.

(Slide) This slide gives you some idea of the reliability of gastroscopic examination, particularly after it is done for some little time. Here the gastric specimens of 30 persons who had been gastroscoped were examined microscopically. The specimens obtained at necropsy were from stomachs fixed with formalin immediately after death, while those obtained at operation were fixed immediately after surgical removal. Histological examination of the stomach was normal in 4 of 5 instances where we considered the stomach to be normal gastroscopically, while chronic gastritis was found in the fifth. We obtained confirmatory evidence by histological examination in each of 3 cases of atrophic gastritis diagnosed gastroscopically. Histological confirmation was also obtained in 5 instances of so-called superficial gastritis and 2 instances of hypertrophic gastritis. In 8 cases of both gastric carcinoma and atrophic gastritis there was histological verification in 7; in 1 of these, patchy atrophic gastritis was seen gastroscopically in a part of the stomach not removed at operation. In 7 cases in which we saw a gastric carcinoma without gastritis there was microscopic verification of the presence of both lesions in 5. In 1 instance the gastritis was distal to the tumor and could not be seen while in another it was overlooked.

(Slide) This is an example of a patient seen on April 1, 1938, with pernicious anemia and diffuse atrophic gastritis, a red count of 1.2 million, and a hemoglobin of 6 gm. per 100 cc. of blood. Treatment was started immediately, and on May 1, 1938, the red count had risen to 2.9 million and the hemoglobin to 10 gm., and there was some improvement in the gastritis. On June 3, 1938, the red count was 3.9 million and the hemoglobin 11.4 gm., and the mucosa appeared entirely normal. I call your attention to the fact that the tongue remained smooth in this patient despite the apparent regeneration of the gastric mucosa (as seen gastroscopically).

I call your attention to another point, the patient's age. He was 81 years old. In spite of this, the mucosa apparently regenerated presumably through the supply of a factor (or factors) in which the patient was deficient.

I should have said that this has not been our experience invariably in 15 cases of pernicious anemia which we have followed. In some cases the gastritis may persist in spite of adequate specific antianemic therapy. In one instance it seemed to actually progress under treatment. This patient had a superficial gastritis when first seen, and later, in spite of return of the blood count to normal and typical clinical improvement, the gastritis progressed as evidenced by the appearance of atrophic changes. This suggests that the mechanism of the gastritis in pernicious anemia may not always be one of dietary deficiency. Apparently in some instances there may be an inflammation of the gastric mucosa which progresses irrespective of treatment.

(Slide) We have observed regeneration of the atrophic mucosa in the presence of hypochromic anemia following administra-

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tion of large doses of iron, suggesting that in some instances the gastritis may possibly be due to a deficiency of iron. Similar observations have been reported by Schindler, Lehman, and others. In this particular case the patient was on a Sippy diet. We did not want to give an adequate diet for fear that we might be introducing an additional variable.

For several years we have studied and are still observing patients with atrophic gastritis without pernicious anemia, hypochromic anemia, gastric cancer, or other gastric disease. The early part of this year we reported five such cases to whom we had given large doses of ventriculin (hog-stomach extract, up to 60 gm. a day). We reported regeneration of the atrophic gastric mucosa following such treatment, suggesting that the atrophic gastritis in some of these patients may be caused by a lack of substance or substances contained in hog-stomach extract.

Here is one such patient. He had diffuse atrophic gastritis on April 19, 1937. He was 78 years old and had had digestive symptoms for 15 years. He was put on hydrochloric acid and a bland diet. When he was regastroscoped on June 18, 1937, he still had diffuse atrophic gastritis. He was then put on 30 gm. of ventriculin a day, starting June 18, 1937, and on November 1, 1937, there was less atrophy of the mucous membrane. Ventriculin was increased to 45 gm. a day beginning November 1, 1937, and on January 14, 1938, his stomach appeared normal. I might add that his symptoms disappeared but that the achlorhydria, which had been present before treatment, persisted. With regeneration of the mucous membrane as seen gastroscopically there may be no return of free hydrochloric acid.

Ventriculin was then withdrawn on January 14, 1938, and on May 16 he had evidences of superficial gastritis and patchy atrophic gastritis. A year later he was back to where he started.

We have made similar observations in a number of cases so that we believe that possibly this does represent cause and effect and not spontaneous change. We admit, however, that more control observations on the natural course of atrophic gastritis are necessary.

(Slide) In cases of atrophic gastritis we have found, as have Dr. Schindler and his associates, that free hydrochloric acid is frequently present and that there is no relationship between the presence or absence of hydrochloric acid and the blood count. On the other hand, when post-histamine achlorhydria is present, one is apt to find gastritis as this slide will show. Of 39 cases of post-histamine achlorhydria, 23 had atrophic gastritis; 9, superficial gastritis; 3, hypertrophic gastritis, and 4, a normal stomach.

(Slide) The observation of Usland, which Dr. Rhoads quoted, has interested us very much. We decided to see if there actually was a relationship between gastroscopically demonstrable gastritis and a long-standing history of digestive distress in cases of gastric carcinoma. Usland's observation, of course, led to the assumption that the long-standing gastric distress in patients with gastric carcinoma was due to a pre-existing gastritis. Our observations failed to substantiate this claim. There was a history of digestive distress for 12 months or longer in 8 of 22 cases in whom we found no gastritis gastroscopically. We obtained a history of digestive symptoms of less than 4 months' duration in 6 of 15 cases with gastritis and gastric carcinoma. We believe, therefore, that the assumption based on Usland's observation is not substantiated. I might add that these observations on gastritis and gastric cancer have been made in 40 cases, proved either by necropsy or operation. More

clinical observations checked by gastroscopy and microscopic studies are necessary in this connection.

(Slide) One will find there is no direct relationship between the duration of symptoms in cases of gastric cancer and the presence or absence of free hydrochloric acid in the gastric contents.

(Slide) The relationship of atrophic gastritis to free acidity in gastric cancer. You see that one may find achlorhydria in the absence of any gastritis demonstrable by gastroscopy. This observation is in keeping with Dr. Brunschwig's observations given yesterday. When gastritis is present, achlorhydria is also apt to be present.

(Slide) Relationship of atrophic gastritis to anemia in gastric cancer. One finds that one may frequently get anemia in the absence of any gastritis. I think that is to be expected when one thinks of the mechanical blood loss which may occur as the result of ulceration. There are probably other factors to explain this anemia.

(Slide) The relationship of the anemia and gastric acidity in cancer. You see that in the absence of free hydrochloric acid anemia is more often encountered than in the presence of free hydrochloric acid.

(Slide) This bears out what Dr. Brunschwig said yesterday, that there is no direct relationship between the location of the cancer and the presence or absence of gastric acidity.

(Slide) One sees here that there is no direct relationship between the anemia and the location of the gastric cancer.

We realize that these observations are made on a relatively small number of cases (40 in all) and feel that a good many more observations are necessary in order to test their validity as well as to throw additional light on the nature of the gastritis that is seen associated with gastric cancer.

Dr. Schindler: Only a few words on the frequency of atrophic gastritis in gastric carcinoma, and some statistical data on the occurrence of benign tumors in all patients observed with atrophic gastritis and with pernicious anemia.

Gastroscopic and microscopic studies were made in 49 cases of gastric carcinoma. In 2 cases the carcinoma infiltrated all portions of the gastric wall; but in 47 cases a study of noninvaded mucosa was possible. In 33 cases distinct gastritis was found, usually of the atrophic type; but in 14 cases a normal mucosa was observed. Therefore, it is difficult to believe that all cases of carcinoma develop on the soil of gastritis. However, as I said yesterday, in some cases we have evidence that chronic gastritis preceded the development of the carcinoma.

Thirty-six cases of solitary or multiple adenomas were observed gastroscopically. Their gastroscopic appearance was characteristic. In 10 cases the mucosa appeared to be normal. In 26 cases a definite gastritis was found, usually atrophic in character (20 cases); 2 were superficial, and 4 were hypertrophic.

These 36 cases were observed in a total of 2,167 patients. In patients suffering from abdominal distress, therefore, benign adenoma is found in 1.65 percent. Among these 2,167 patients were 310 cases of uncomplicated atrophic gastritis; 15, or 4.8 percent of these patients, had adenomas.

In 43 patients suffering from pernicious anemia, adenomas were found 6 times, an impressive percentage of 14. I may add that in 2 of these 43 patients a carcinoma developed. But I am not sure whether this figure is sufficient to state a causal connection; while on the other hand the figure of 14 percent for benign tumors is very suggestive.

The close connection between atrophic

gastritis and benign adenoma becomes still clearer from the following data: In 1,814 patients who did not have atrophic gastritis only 15 adenomas (0.83 percent) were found; whereas among 353 patients who had atrophic gastritis, 21 had adenomas—that means 6 percent. In the second group adenoma occurred 7 times more frequently than in the first.

Dr Rhoads: It seems to me that the very important observations of Dr. Schiff and Dr. Schindler bear out to some extent the speculations that I presented. No one would maintain for a moment that all gastric cancers develop on a basis of gastritis. If one can show, however, that any gastric cancer so develops, that fact at least provides us with a tool for further study of preventive methods.

The failure of any one to produce chronic gastritis experimentally is a serious objection to the concept of gastritis as a deficiency disease. We tried to cause gastric lesion by feeding experimental animals on diets lacking in that vitamin B complex which seemed to cure or improve the gastritis of pernicious anemia and of sprue. We did not see histological changes. A similar observation has been made by Dr. Wintrobe, of Baltimore. However, we are not sure that the ideal experimental conditions have been observed. It does seem to me that the great lack of the present time is the ability to produce experimentally a chronic degenerative disorder of the gastric mucous membrane, and if this series of communications has any value, I hope it will be to stimulate work on this subject.

Chairman Hektoen: The next paper is The Use of Clinical Material for the Investigation of Gastric Cancer, by Dr. Mont R. Reid, Professor of Surgery, University of Cincinnati College of Medicine.

The Use of Clinical Material for the Investigation of Gastric Ulcers

By Mont R. Reid, *Christian Holmes Professsor of Surgery, University of Cincinnati, College of Medicine*

INTRODUCTION

Only in recent years has the medical profession begun to realize that the study of human material may approach in accuracy and controlled conditions the study of laboratory animals in the investigation of many problems. This has been due in large measure to two things: (1) The antipathy toward the use of human beings for the investigation of research problems is rapidly disappearing; and (2) improvements in the methods of technique, both physical and chemical, have made it possible to make vastly more accurate observations, under controlled conditions, upon humans without in any way jeopardizing human life or of subjecting the investigators to the accusation of inhuman or cruel practices.

With this change in attitude toward the use of human beings for investigative purposes there has resulted not only an improvement in the results of the therapy of the condition under investigation, but also the realization that one can find the condition and related conditions in a variety of stages which are almost impossible to reproduce in laboratory animals. In other words, modern conditions make it not only justifiable but mandatory to attack the actual problem as it exists in human beings much more vigorously and directly, as well as through the medium of laboratory animals.

In this paper I shall endeavor to describe our work and our plans for the investigation and treatment of gastric cancer in human beings. It seems to me that the best approach to this information is to tell you first what we have done so far.

WORK AT THE GASTRIC-CANCER CLINIC

For many years there has been, as there is in most medical clinics, an outpatient gastric clinic at the University of Cincinnati. In it are carried out the routine diagnosis and treatment of gastric disorders in charity patients. It is a large clinic, and little time is left for other than the routine care of patients. In 1936, through the efforts of Dr. Leon Schiff, a gastric laboratory was started in which it was proposed to make careful clinical research studies upon cases selected from the large dispensary gastric clinic. Inasmuch as cancer of the stomach was one of the main conditions selected for investigation, the cooperation of the tumor clinic, which handles all cases of malignancy, was soon brought into the plan. Other conditions were selected for study, as time went along, were chosen largely from their possible etiological bearing upon gastric carcinoma. They were cases of peptic ulcer, atrophic gastritis, achlorhydria, and pernicious anemia.

At first the work consisted of very complete clinical histories, carefully controlled chemical analyses of the gastric contents, and repeated fluoroscopic and X-ray studies to observe the progress of nonmalignant conditions. The effect of certain forms of therapy upon peptic ulcer was evaluated in this laboratory, for example, the use of silicon dioxide and the Muhlengracht diet.

In a short time Dr. Schiff requested the aid of a surgeon in this study, and Dr.

Zinninger, of my department, took over that responsibility. A pathologist and a roentgenologist were next added to the team of clinical investigators of this problem. Finally, the plan was extended so that every resident in both medicine and surgery must at some time during his training participate for a period in the work of this laboratory. The source of supply of human material was extended to include any gastric case in the hospital, as well as the outpatient clinic, which Dr. Schiff or Dr. Zinninger might desire for investigation.

This laboratory operates daily, except Sunday, throughout the year. In it there are a "diener" (laboratory helper), a chemist, a secretary, and a graduate fellow in medicine, all on full-time duty. On part-time duty are an artist and a dietitian. These are all in addition to Dr. Schiff and the representatives of the various departments I have mentioned above, who give generously of their time to this work each week. From an educational as well as a scientific point of view, the formal conferences which are held once a week are of the greatest value. At them all cases under investigation are frequently and carefully reviewed, and the internist, the surgeon, the gastroscopist, the roentgenologist, the pathologist, the fellows, and residents help to assay the information which has been gained about each patient. As you can imagine, many people are frequently put on the spot, as I shall show you later when I attempt to give some of the results of these investigations.

A great stimulus to the work in this laboratory was the acquisition of a gastroscope. Last year, through the aid of a grant from the National Cancer Institute, we were able to secure another and more modern one.

With the introduction of the gastroscope came the necessity of a medical artist who might reproduce accurately what was seen with the eye so that these views might later be compared with photographs and drawings of specimens obtained at operation or autopsy. At the beginning, this seemed to be the quickest way of learning how to interpret what was being seen through the gastroscope. With the experience we have now gained, the gastroscopist is rarely in doubt as to the nature of the lesion he is seeing and this function of the artist is no longer so important. However, these illustrations are extremely valuable in recording the progress of therapy upon nonoperative conditions such as peptic ulcer and gastritis which may prove to be precancerous lesions. As we have heard today the introduction of actual photography may displace the need for such an artist.

In this laboratory, for the investigation of gastric cancer Dr. Schiff and his assistants have now made 858 gastroscopic examinations.

Another departure which has led to considerable interest has been a different approach to the study of the pathology of gastric cancer and possible precancerous lesions. For several years, through the aid of the National Cancer Institute, we have had a technician who, along with other duties in connection with our tumor clinic work, has been making large microscopic sections of all of our neoplastic growths. By way of parenthesis, I may say that every surgeon we train receives, at some time in the course of his 6 years, at least 6 months of intensive training in our tumor clinic where he gets experience in the radium and X-ray therapy of cancer. In connection with the training of these surgeons and the teaching of medical students, we have found these large microscopic sections a most valuable aid. In the gastric-cancer problem we have found these large sections obtained either by

operation or autopsy of the stomach at different levels to be most illuminating. The work began with the idea of determining the existence of any basic pathology which might have been present in the stomach before the development of the carcinoma. In many cases there does exist a chronic inflammatory process, as evidenced by scar tissue and mononuclear infiltration, through the stomach, far removed from the carcinoma. We have learned also that the carcinoma frequently extends far beyond the ability of the eye or finger to detect. This knowledge alone is of great importance to the surgeon in the operative treatment of gastric cancer.

This line of study has also started us on a program of making large sections of the stomach in cases of chronic gastritis, achlorhydria, etc., as well as sections of the stomach of apparently healthy people at different ages of life. This, in time, may give us some idea of the stomach's response to incessant activity and the irritation of certain kinds of food which have been favorites of the different individuals.

In order to make these studies, one has to be prepared to fix the stomach with formalin solution immediately after death. We have found that this can best be done by inserting a needle into the stomach through the eighth and ninth interspaces in the anterior axillary line and through the abdominal wall an inch below the xyphoid process, pointing the needle upward and to the left. A lumbar puncture needle attached to a 50-cc. Luer syringe is used, a total of 500 cc. of 10-percent formalin solution being introduced. The necessary materials are kept at convenient places in the hospital so that the fixing can be done without delay regardless of whether permission for an autopsy may or may not be obtained. It is obvious that in our endeavor to secure apparently normal stomachs, specimens must be obtained from individuals who die from accidental deaths, for chronic diseases and acute infectious processes alter materially the histologic picture of the stomach.

Another line of investigation now in progress is a careful study of the dietary habits of gastric-cancer patients. For this purpose a dietitian makes a careful record of each patient's habits respecting foods, noting particularly the kinds of food, the predilection for excessively hot things, the use of alcohol, condiments such as pepper, meats, vegetables, thorough mastication or bolting of foods, etc. Obviously such a study will take years to be of any value.

Of particular interest to us has been a study of the relationship of chronic gastritis to the various problems of gastric cancer. As I have said before, such cases are constantly being observed for the development of cancer. In a given case of cancer we endeavor to evaluate this condition (1) by a careful history of symptoms of gastritis prior to the development of the cancer, (2) by the gastroscope and X-rays, and (3) by microscopic sections of material obtained at autopsy or operation. Microscopic sections are taken from various levels, through the base of the tumor and along the lesser and greater curvatures. Thus far it is difficult to draw any conclusions. In many instances it is difficult for us to evaluate the role that chronic gastritis may be playing in the so-called symptoms of gastric cancer. The anemia, the achlorhydria, and the general nutritional state of the patient may be more a result of this condition than of the carcinoma itself. In fact the carcinoma *per se* appears to us to cause very little general nutritional disturbance unless it produces pain, bleeds, or interferes mechanically with the functions of the stomach or other abdominal viscera.

Whatever the cause, it has become increasingly important, from a practical

point of view, to make a careful appraisal of the nutritional state of all gastric-cancer patients. The days of operating as soon as a diagnosis is made or because obstruction exists should be over for all surgeons. There is never such a hurry that certain vitamin deficiencies and nutritional disturbances cannot be determined, and with our modern means of therapy, to a large extent corrected. From the blood the status of vitamins A, C, and K can be determined, and from the urine there appears to be a fairly reliable method of determining the deficiency of vitamin B. The state of the blood, particularly with reference to the red blood corpuscles, the hemoglobin, and serum proteins, should be known. The fluid balance of the patient should be determined.

The restoration of a normal fluid balance, the administration of needed vitamins, particularly vitamin C, and the use of blood and plasma to correct the anemia and hypoproteinemia can be accomplished in a relatively short time and will greatly reduce the hazards and mortality of operative therapy. It is now inexcusable not to pay attention to these things in all forms of surgery, but particularly in the case of gastric cancer when the nutritional state may actually be that of a severe case of pellagra.

I have endeavored to outline to you the various lines of study upon human beings which our interest in gastric cancer has taken. I shall not attempt to evaluate those studies from the standpoint of the etiology of gastric cancer for as yet we have no information which we regard as significant. However, from a practical point of view, there have come out of these studies certain observations which are extremely important in dealing with the problem as we know it today.

In the first place, this interest in the problem has resulted in earlier diagnoses and a steady rise in the operability of our cases. In the 5-year period (1932–1936, inclusive) the incidence of resective operative procedures was 3 percent, while in the 3-year period (1937–1939, inclusive) it was 23 percent. These figures, though showing an improvement, are most discouraging; but it must be remembered that they are based entirely upon a study of free, charity patients in a large city hospital, where it has been rather the rule to see all sorts of medical and surgical conditions in advanced stages when first the patients present themselves.

Any study of the duration of symptoms has been most difficult to evaluate, inasmuch as the symptoms of chronic gastritis, which frequently accompanies carcinoma, may very accurately simulate those of actual carcinoma.

The gastroscope has been of the greatest aid in determining the true nature of ulcerative lesions of the stomach. While X-ray studies may show that such a lesion exists, they frequently leave grave doubt as to whether it is benign or malignant. In fact, before the introduction of the gastroscope the behavior of such a lesion under therapy, as determined by X-ray studies, was often the only guide as to the probability of malignancy. If the lesion showed evidence of healing under the treatment it was regarded as benign; if not, or if it enlarged, it was considered as likely to be malignant. Under such criteria it is obvious that much valuable time was frequently lost. The gastroscope has almost entirely eliminated such uncertainty when the lesion is in a site which can clearly be visualized. Furthermore, we have seen with the gastroscope ulcerative lesions decrease in size under therapy when carcinoma was present in the rim of the ulcer. In one such case the symptoms of ulcer for a time disappeared, and the patient gained weight even while the

carcinomatous area in the rim of the ulcer was slowly progressing. So now chronic ulcerative lesions of the stomach which cannot be visualized with the gastroscope are regarded with the greatest concern even though symptomatically they appear to be improving under therapy.

The fallibility of all of our present methods of diagnosing early carcinoma of the stomach has been strongly impressed upon us. Certainly the days of accepting a negative report on X-ray studies of the stomach as a postitive proof of the nonexistence of carcinoma are over. In a series of 40 carcinomas of the stomach proven by operation or autopsy, X-ray studies have failed to show any evidence of a pathologic lesion 5 times and have led to a diagnosis of benign lesion 5 times.

The supplementary value of gastroscopic and X-ray studies can be shown by the following figures: In 6 cases when the diagnosis could not be made by X-ray studies, it was definitely made by gastroscopic studies. In 6 cases when the gastroscope revealed no malignant lesion, the X-rays were correct in making the diagnosis. In 25 cases the presence of a malignant lesion was determined both by X-rays and the gastroscope. I wish you to note, however, that there were 3 cases in which the diagnosis could not be supported either by gastroscopic or X-ray studies. It appears obvious to us that the X-rays have been especially accurate in diagnosing far-advanced lesions, and that, if we hope to make earlier diagnoses, the importance of the gastroscopic studies will greatly increase for they show the early lesions which are more likely to be missed by X-ray.

In support of what I have been saying I wish to cite two cases:

On January 30, 1940, a 74-year-old woman entered the hospital with serious gastric symptoms which were very suggestive of carcinoma. These had been present since October of the preceding year. However, on careful questioning, her symptoms appeared to be only an exaggeration of episodes of gastric distress during the past 30 years. She called them "dyspepsia," but they were frequently accompanied by emesis and diarrhea. Throughout this time she was suspected of having a peptic ulcer, but X-ray studies 16 and 6 years ago were entirely negative. Her present symptoms seemed to her to be only an exaggeration of her old symptoms with the exception that, for the first time in her life, she was having pain. Thus, on careful analysis, it was only pain which made her date her symptoms of onset back only 3 months. A week before she came to the hospital, some X-ray studies, made in Macon, Ga., seemed to indicate that she had a carcinoma of the stomach. She was also told that she had "no acid in her stomach."

We found her in a state of good general nutrition.

Repeated X-ray studies failed to reveal any findings which were compatible with carcinoma. There appeared to be some deformity of the pylorus which was thought to be either due to an old ulcer or to a congenital deformity. However, the stomach seemed to be functioning normally. There was no free hydrochloric acid, but the combined acidity ranged from 16 to 65 percent. The stools were free of blood.

Finally a gastroscopic examination revealed a small lesion on the lesser curvature of the stomach, well proximal to the pylorus. This was thought to be a scirrhus carcinoma. Without this study there is no doubt that this patient would have been returned home without any operative therapy.

A large gastric resection was done. The carcinoma was on the lesser curvature

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about 2 inches from the pylorus. The ulcerated area was very soft and shallow and only about ¾ inch in diameter. There were no visible metastases, and the immediate glands were not involved. The rest of the stomach showed a high-grade atrophic gastritis which undoubtedly explained many of her symptoms over the long period of years.

The next case is that of a 63-year-old lawyer, with gastric pain and distress of 4 months' duration. Studies during this time revealed a solitary gallstone, a diverticulum of the duodenum, and multiple diverticula of the colon. In all there were four X-ray studies made of the stomach without revealing any pathologic lesion. There was plenty of acid in an analysis of the gastric contents. Some blood was found in both the gastric contents and the stools. Through the gastroscope no pathologic lesion was seen in the stomach. It was thought the patient might have an ulcer in the cardiac end of the stomach or possibly that his symptoms might be due to the duodenal diverticuli.

After failure of the patient to respond to any kind of therapy, an exploratory operation revealed a totally inoperable carcinoma of the cardiac end of the stomach.

What I have been saying here strongly supports the point which every doctor admits, but which many do not observe, namely, that no diagnostic laboratory test is infallible, and that all of them must be doubted when they run counter to an opinion based upon a good history and sound clinical judgment. Cincinnati is in line with the conclusion reached by Cooper at the New York Hospital. Many patients have lost their chances of life because of a single laboratory test which failed to comfirm the physicians' suspicions of a malignancy of the stomach. This is no excuse for dropping the matter and assuring the patient that nothing is wrong. It is admitted that the triple check of gastric analyses, X-ray, and gastroscopic studies rarely fail to give the clinician sufficient backing to arrive at a correct diagnosis; but when they fail to back his sound clinical judgment, the physician has no right, in the light of our present knowledge, to dismiss the matter from his mind. These studies should be repeated as often as necessary until there exists little or no doubt but that they should take precedence over clinical judgment. In some instances I have operated in the absence of any support from these various tests and found carcinoma of the stomach. In other words, these laboratory aids to the diagnosis of cancer, like so many other tests, have a far greater positive than a negative value.

In our experience it should be stated that X-rays most frequently fail to reveal lesions on the lesser curvature of the stomach about 2½ inches from the pylorus, while the gastroscope is least helpful in diagnosis of lesions at the pylorus or in the cardiac end of the stomach.

During the past 3 years we have been following 10 cases of chronic atrophic gastritis. About every 4 to 6 months each patient has been subjected to a complete study, consisting of chemical analyses of the gastric juice, and X-ray and gastroscopic studies. On these patients alone there have been made 64 gastroscopic studies. To date we have not seen one of them develop a gastric cancer. We have also had under observation 40 cases of achlorhydria and have not seen one of them develop carcinoma.

Repeated gastroscopic observations of chronic peptic ulcers of the stomach give us much greater assurance as to the therapy of this condition than we have ever had before. In this way the doubt as to the effect of therapy or the developing of a

carcinoma can be very largely eliminated.

We are cognizant of the great arguments regarding the development of carcinoma in chronic peptic ulcers of the stomach. Our sympathies, however, are with those who believe that chronic gastric ulcers, which fail to respond to therapy, should be regarded as precancerous lesions. We teach that chronic sores and ulcers on other parts of the body surface may develop into carcinoma; the malignant Marjolin's ulcer is a case in point. It seems illogical to us that a chronic ulcer or sore of the stomach may not show the same tendency. The following case, bearing on this subject, while not in any way conclusive, is interesting.

A 41-year-old white female came to the hospital in 1936, complaining of vomiting blood and the passing of black tarry stools. For 8 years she had had epigastric pain occurring immediately to 1 hour after meals. This was relieved by food, milk, and alkali. There was a definite history of exacerbations of her pain in the spring and fall.

In August 1937 there was an anterior perforation of a gastric ulcer, treated by simple closure.

On March 1, 1938, roentgenographic studies showed a large ulcer crater on the anterior wall and lesser curvature of the stomach. On March 8, 1938, gastroscopy showed a benign penetrating ulcer on the anterior wall near the lesser curvature. A month later gastroscopy showed the ulcer greatly reduced in size. On June 14, 1938, the ulcer was still very small.

On May 2, 1939, roentgenographic studies showed the ulcer still present. On June 12, 1939, gastroscopy showed the ulcer much larger and resembling its appearance when first seen in March 1938.

During the summer of 1939 she was practically free of symptoms, but in the fall the pain returned and was more frequent and more severe than ever before.

The patient was admitted to the hospital on March 21, 1940. The studies showed a typical carcinoma at the site of the ulcer. This was proven by a gastric resection which was done on April 8, 1940.

Our results of repeated chemical analyses of the gastric juice in cases of ulcer and carcinoma of the stomach confirm the results obtained by Cooper and many others. While extremely helpful in most conditions, they cannot be regarded as pathognomic of the exact condition present. In 11.4 percent of the cases of gastric carcinoma the acidity was found to be within the normal range. In 28.5 percent it was subnormal, and in 60 percent there was no free acid. It also must be remembered that an occasional ulcer case will reveal no acidity.

Our experience with X-ray therapy of gastric cancer has been rather unfortunate. In several cases we feel that we have hastened death by causing a perforation of the stomach.

CONCLUSIONS

1. It is desirable and justifiable to use human beings for the study and investigation of gastric cancer. It offers a different approach to the problem and in many respects a more important one than by the use of laboratory animals.

2. A group of doctors, properly selected for the study of this problem, is most beneficial to any clinic, hospital, or university. It results in earlier diagnosis, and better medical and surgical care. From many groups of this kind, thus attacking the problem, there cannot help but accumulate information which will be of great importance in our efforts to deal with this problem.

3. The coordinated use of the gastroscope, X-rays, and carefully controlled chemical studies increases tremendously

the effectiveness of our present means of combating this problem.

4. The nutritional state of all gastric-cancer patients should be carefully assayed and, if possible, corrected before attempting any therapeutic measures, especially surgical procedures.

5. In our clinic we are especially interested in the possible relationship between gastritis, achlorhydria, anemia, and chronic gastric ulcer to gastric carcinoma.

6. We also believe that a careful study of what is put into the stomach may eventually throw some important light upon the etiology of cancer of the stomach.

7. Careful histologic studies of the stomach by means of large microscopic sections will not only result in more effective surgical procedures but may be very helpful in determining the underlying changes which precede the development of carcinoma.

8. At present all laboratory tests should be evaulated for what they are worth, and no more. They have a far greater positive than negative value. A good clinician will not be easily swayed by them when they run counter to his clinical judgment.

DISCUSSION

Chairman Hektoen: Dr. Rhoads will open the discussion of Dr. Reid's paper.

Dr. Rhoads: I should like to express my appreciation to Dr. Reid for this paper. When I saw his manuscript some days ago I was very much impressed by the fact that Dr. Ewing and I at Memorial Hospital had been trying to set up an organization for the study of clinical material which was almost identical with that of Dr. Reid.

I think I have little to add. We have been thinking along precisely the same lines as those just presented. We have arranged, with the aid of the philanthropic foundations, a series of laboratories which we hope will give us information concerning the metabolic disturbance present in a patient with supposedly precancerous lesions. In our chemical laboratory, studies of phosphorus metabolism and of sodium and potassium balances are in progress, because we are looking for a reflection of disturbed sterol metabolism in patients with gastritis. Our vitamin laboratory aids in exploring the nutritional status of the preoperative and postoperative problems, and also provides information concerning the nutritional basis of what we think to be precancerous changes of the mouth and the gastrointestinal tract.

Our enzyme laboratory studies those enzymes of which the known vitamins form an essential part, in the hope that we can isolate such enzyme systems as control the sterol metabolism. Our hormone laboratory studies the metabolism of the sterols known to be biologically active in the patients with cancer and precancerous lesions. A sterol chemist with his group and a spectroscopist with his assistants aid in the isolation of sterolic substances which have not been proved to be active as sex hormones. The team is new, but it has obtained the cooperation of the clinical men and has been able to help them with their problems.

As we see the organization straightening out, we see certain factors of interest developing; and I hope we can prove, as Doctor Reid has proved already, that the answer to this very grave problem will be cooperative scientific investigation.

Chairman Hektoen: The discussion will be continued by Dr. Morton.

Dr. Morton: It is always a pleasure to hear Dr. Reid. He is a sound man, and I am glad to hear anything he says at any time.

I think it is apparent that the problem of clinical investigation of cancer is one that cannot be carried out by a single service in

any hospital as now organized. I think that it also becomes perfectly apparent that such an investigation cannot be carried out in an outpatient clinic where the endeavor is to clear the outpatients, to get the people through as expeditiously as possible, without taking time for investigation. As far as any real clinical investigation is concerned, it will call for an organization and a group of free beds where patients can be hospitalized and studied.

When Dr. Reid sent his paper to me, I was much impressed by his organization. He has plenty of help, and with that he can do a good bit of work which the ordinary clinician cannot do by himself.

A couple of years ago it became apparent to us that we needed a gastroscope, so the medical and surgical budgets were tapped and we bought one. Our experience with the gastroscope has been practically identical with Dr. Reid's. There are six doctors in attendance at the gastrointestinal clinic. We are trying to make more than one person familiar with the use of the gastroscope. We think it will be a necessary procedure to train more than one man, because oftentimes men are away or sick and we should have someone to replace them. There is no man in our clinic who cannot be replaced.

Perhaps we could expedite the work if we had fluoroscopic apparatus right in the gastrointestinal clinic. This was taken up with the X-ray department of the hospital, with respect to the possibility of sending one of their men down to the gastrointestinal outpatient clinic where the patient could have a fluoroscopic examination, but no elaborate pictures taken, as is necessary at present in a complete gastrointestinal series. In that way it would be possible to investigate people with gastric symptoms more than once and at a minimum expense. The normal stomach is easy to identify if you have had any experience at all with fluoroscopic investigation. Medical men and surgeons would be much more interested in the investigation if they took part in the actual diagnostic procedure.

When Dr. Reid talked about large microscopic sections, I thought at first that this would probably not give us much information on the etiology of gastric cancer. The method has been used a good many times. The whole-organ sections are very pretty, excellent for orientation when you have the microscopic sections, and, as Dr. Reid has explained in this paper, if you can show where the section comes from it makes it much more interesting. These sections are certainly good for teaching, and they furnish a marvelous orientation as to the exact location of the lesion.

In regard to the teaching of gastroscopists, I think it will be necessary for somebody to publish an atlas of colored plates representing conditions found through the gastroscope. I do not see why this would not be a function of the National Cancer Institute. This Institute might very well put out such an atlas which would be available to people beginning the study of these problems through gastroscopic methods.

In regard to further studies on the enzyme systems, the deficiency states, and so on, I will speak about them when I discuss Dr. Voegtlin's paper.

Chairman Hektoen: Discussion on Dr. Reid's paper will be continued by Dr. Dochez.

Dr. Dochez: I think it is probably a little presumptuous of me, a bacteriologist, to discuss the problem of cancer, but I have for many years been associated with the medical clinic and have always been impressed—depressingly impressed, I may say—by the lack of any constructive interest in departments of internal medicine in the problem of cancer. In fact, after long association with two rather

large societies made up almost exclusively of internists, I have difficulty in recalling any discussion of the problem of cancer; they seem glad to turn it over as quickly as possible to the surgeons or the radiologists.

It is indeed encouraging to learn from Dr. Reid's paper how thorough and competent an organization for the study of cancer can be built up within the field of action of a general hospital clinic. Such a clinic comes to possess and control a clientele representing all stages and many varieties of gastric disease, and makes possible the all-important extension of the period of observation over sufficient lengths of time to test adequately the validity of any conclusions that may be arrived at. The great weakness of many hospital clinics is perhaps of necessity the episodic character of such studies as may be undertaken. The evolution of disease takes place over periods of time, in some instances of long duration, and unless a mechanism is in operation which takes account of the time factor, a complete picture of the disease process with the interrelated clinical episodes cannot be obtained.

Another most important service of such a clinic is the availability for consultation, interpretation, and investigation by a group of highly trained specialists of such suggestive observations as present themselves for consideration from time to time. We are all familiar with the type of clinic many times conducted by capable and observant men who are competent to detect the interesting and suggestive phenomena of disease, but in which no mechanism exists for the following up and correlating of such observations as are recorded. An organized purpose gives permanence and constructive value to casual observations by relating them to the collective experience of the group as a whole. Only in such a way can the final pattern of a disease be clearly discerned.

For a number of years we have regarded as a matter for very serious thought the failure of departments of internal medicine to concern themselves with the problem of cancer as a major investigative undertaking. In general, in the medical clinic cancer presents itself and is mostly considered as a problem in diagnosis. Once the diagnosis is made, further responsibility, largely therapeutic in nature, is transferred to the surgeon or the radiologist. Such patients as are not suitable for transfer—and they constitute, I think, a considerable proportion of all cases—are cared for in a routine manner, by using whatever palliative procedures are available. As a rule, no organized effort is made to develop a constructive undertaking which would collect and analyze the data derived from patients suffering from cancer, to say nothing of the development of a plan that would outline the kind of knowledge which it is desirable and important to obtain.

In contrast to this approach, internal medicine has undergone, during the last 25 years, an extraordinary evolution in the methods of dealing with many of the common problems of disease with which it is confronted. The development of exact scientific procedures in the fundamental medical sciences has engendered a similar movement in internal medicine which, in some respects at least, may be considered as an almost revolutionary approach when compared with the simpler clinical techniques of the past. There are few important medical clinics in this country which have not organized special investigative groups with extensive facilities for the intensive and long-time study of the special problems of internal medicine. I need only mention such undertakings as the investigation of the pathological physi-

ology of the circulatory and respiratory systems, renal diseases, disorders of the glands of internal secretion, nutritional abnormalities, diseases of the blood, and even groups for the study of specific diseases such as chronic arthritis, rheumatic fever, pneumonia, and a number of others.

This kind of approach to the study of disease has led to the development of a new type of clinician, or perhaps I might better say, clinical investigator. The younger men combine within themselves both clinical training and acumen and at the same time a background of experience in scientific procedures and specialized scientific knowledge which enables them to deal with the most complex biological questions in a thoroughly competent and productive manner. Such groups also contain within their personnel highly trained specialists in chemistry, physiology, bacteriology, and other related sciences. These latter individuals give advice about, or may even take over, such problems as arise which require the most highly specialized and individual knowledge for their solution. The productive output of such groups has been important and large in amount and need not be mentioned in detail.

For a number of years it has seemed to me to be a matter of great concern that departments of internal medicine have not been active in organizing a similar group for the purpose of studying cancer. Perhaps they have considered the problem too difficult, but that can hardly be an adequate answer. Therefore, it has seemed to us that the time has come for internal medicine to assume some of the responsibility for the study of cancer and to approach the problem with the same thoroughness and long-time outlook that has developed in respect to other disease problems within the field of internal medicine. At the Presbyterian Hospital in New York we have recently inaugurated such an undertaking; we have been trying for the last 2 or 3 years to stimulate such an interest, to try to get the clinicians, particularly the clinicians who are devoted to the study of disease, interested in the problem of cancer; and it has at last come about that we have been able to start in a very small way. The scope of the study in the beginning is very limited, of necessity. We hope by it, however, to stimulate interest, to develop a spreading consciousness of the problem, and in this way to lay the foundations for a comprehensive and perhaps fruitful investigation.

I realize that I have dealt with this question in a very general sort of way. I am not competent to be specific about it. One would like, of course, to present a detailed plan of approach, if one could think one out; but that, under the present circumstances, I think, in view of the youthfulness of the undertaking, would be entirely presumptuous. I think with a subject as difficult as cancer, all that we can anticipate is that from a number of small beginnings and by stimulating an interest in these problems, new avenues and new approaches to the study may come about. We hope that by planting a small seed in the Department of Internal Medicine at Columbia, it may sprout a little bit and affect some of the other clinicians in the department.

Chairman Hektoen: Dr. Alvarez will continue the discussion,

Dr. Alvarez: One difficulty in this study of cancer is that in spite of the fact that it is a big problem throughout the country, the average physician, even with abundant clinical material, does not in any one year see enough gastric ulcers or gastric carcinomas to learn much about them. That is why I think it might be worth while here to review rapidly the report of a

tremendous study which has just been finished at the Mayo Clinic under the direction of Dr. Walters. Most of the work has been done by Dr. Lewis, who for the last year has spent all day and half the night in the record room reviewing the histories, the operative records, and the postoperative course of 10,890 patients with carcinoma of the stomach seen at the Mayo Clinic in the last 38 years. Of these patients, 6,352 were operated on, and 2,840 had a partial resection of the stomach. There were 3.5 males to 1 female.

Very valuable is this study from the fact that there was a good follow-up of over 99 percent of the patients. As you know, most follow-up studies are largely invalidated by the fact that only some 60 or 70 percent of the patients answer the questionnaire, and one does not then know whether the others are mainly dead or mainly well. Obviously our statistics must be highly erroneous if we have no answer to this question. Now, for the first time the answer is available.

It is interesting to note that of the patients who could have the lesion resected, 55 percent had the usual vague story of indigestion; of those in whom the lesion could not be resected, 65 percent had that type of story. Of those with a lesion that could be resected, 37 percent gave a history of ulcer, fairly typical, either throughout the period of illness or else at some time in it. This, to me, is the most important point to be hammered home here, and I am going to keep hammering at it. Let us never forget that 37 percent of the patients with a resectable lesion had an ulcer story, and, more important yet, 81 percent of the many persons with cancer who were treated for ulcer before we saw them at the Mayo Clinic responded well to that treatment and were thought for a while to be getting well. We will never get anywhere with the early diagnosis and treatment of carcinoma of the stomach until we face these facts. Some able men are not only not facing them yet, but they are greatly confusing the matter by talking about the frequency with which benign ulcers turn into cancers. That is largely an academic question. The all-important practical fact is that today most patients with cancer of the stomach are, for a year, treated by good physicians for ulcers of the stomach.

Twenty-five percent of those persons with a nonresectable lesion gave an ulcer story, and 8 percent had an atypical story. Eighteen percent had had symptoms for 5 years or more, so 82 percent had a short history. Again, we physicians will never get anywhere with our campaign for the early diagnosis or treatment of carcinoma of the stomach until we face the fact that a short history of indigestion in an older man is and always must be an alarming signal. If I had never had indigestion in my life and today were to get symptoms of distress and pain in my stomach, I should want to be X-rayed tomorrow; and if a lesion were to be found, I should probably have it removed surgically next week. That is the only way in which I could hope to save my life. Even then it might well be too late. One of the greatest physicians of his time had had gastric symptoms for 3 weeks and then when he was roentgenoscoped, the lesion was found to be so far advanced he could not be cured by operation. As we all know, this is our main difficulty in diagnosing cancer of the stomach—in most cases the symptoms come too late. In Dr. Walter's series of cases, 45 percent of the patients with a resectable lesion had had symptoms for less than a year. In those cases in which resection was impossible 54 percent had had symptoms for less than a year. That sounds paradoxi-

cal, but again we see that it is the short history that is most dangerous. Perhaps the uncomplaining, or insensitive type of man fails to realize he is ill until the growth has become large and widely disseminated.

Among patients with lesions that were removable, 75 percent had a definite diagnosis of carcinoma made by X-ray; in 13 percent the roentgenologist was suspicious of carcinoma but was not sure; in 99 percent of cases he saw something wrong in the stomach. Today the gastroscopists are helping us. In the old days, before we had the gastroscope, we at the Mayo Clinic had to explore the stomach surgically in one out of four cases in order to give the patient his chance to be cured of cancer of the stomach. This is a fact to keep in mind. One out of four patients with a suspicious something in the stomach had to be operated on promptly in order that he or she could have the diagnosis of cancer of the stomach made in time so that the surgeon could work a cure. If we had waited, many would doubtless have lost their lives.

Of those lesions thought by the roentgenologist to be inoperable, 2 percent were found at operation to be removable.

In 23 percent of the resections the tumor was graded 1 and 2, and in 77 percent graded 3 and 4 on Broders' scale of malignancy. I think Dr. Ewing pointed out yesterday that the grade 1's are not so numerous as we might wish them to be. Of the nonresectable tumors, 7 percent were graded 1 and 2, and 93 percent were graded 3 and 4.

Among the 10,890 patients, 42 percent could not or would not be operated on, which agrees pretty well with the figures given by others. At the Mayo Clinic, 58 percent were operated on, rather more than in most places. In 45 percent of the cases in which exploration was possible, resection of the lesion was feasible. Of the original 10,890 patients, then, 2,840, or 26 percent, were able to have a resection.

The hospital or operative mortality for the whole group for all the years was 16 percent, but it is hopeful to note that this figure dropped to 14 percent in 1938 for about 104 cases, and to 11 percent in 1939, with 131 cases. Sixteen percent of the patients whose abdomens were explored could have only some palliative operation such as gastroenterostomy. Their hospital mortality rate was 12 percent. Those who were just quickly explored had a hospital mortality of 4 percent. As you all know, it is dangerous even to touch these people.

In that 72 percent of cases in which the risk was considered fair, the operative mortality was 10 percent, while in the patients in bad condition or old the operative mortality rose to 28 percent. In the case of those over 60 the operative mortality was over 20 percent, while with those between 30 and 39 it was 5 percent.

The uncorrected 5-year-survival rate for the whole group—and here is something hopeful—was 29 percent. When this was corrected, as it should be, for the number of persons at the advanced average age of these patients who would normally die, one finds a 5-year survival rate of 32 percent, which I think is much more hopeful than any yet reported anywhere.

The 10-year survival rate was 25 percent. Patients with a short history showed a survival rate of 25 percent, while those with a long history showed a rate of 32 percent (5-year survival). This seems at first sight odd and paradoxical, but one can probably explain it.

Here is something that surprises me and makes me happy. I have always felt that a young person around 30 with carcinoma of the stomach might just as well make his will and be left alone to die, but I find now from these Mayo Clinic records

that when the surgeon could resect the lesion the patient had just about as good a survival rate as anyone else. Hopeful was the fact that only 5 percent of these young persons died in the hospital following the operation. This helped to leave many alive 5 years later.

As I remember, yesterday someone was pessimistic about the prognostic value of grading the malignancy of the tumors. I can't be pessimistic, because for years I have been seeing persons with grade 1 tumors live and those with grade 4 tumors die. In this large series of Walters and Lewis, with patients with tumors graded 1 and 2, the 5-year adjusted rate was 68 percent, which is certainly well worth striving for. For persons with tumors graded 3, the rate was 30 percent, and for persons with tumors graded 4 it was 23 percent. There you see a tremendous difference. But even with tumors graded 4 and with some extension to peritoneum and nodes, a number of the patients whose cases we thought were hopeless survived. It is a most remarkable fact that extension, let us say, into the pancreas does not make the case hopeless.

As I see it, one of the first things we must do is to give doctors these figures; they must be encouraged in regard to the treatment of cancer. As someone said at the beginning of the session yesterday, too many doctors say, even when they themselves have a gastric cancer, "Why be operated on? Nothing can be done, there's no hope, no one ever gets well." That is all wrong. The patient might have a tumor of grade 1 or 2 malignancy, and then if it was resectable he would have a 68-percent chance of surviving if he left the hospital alive.

If we want to do something practical now, the first big job is to get doctors to see that every patient with a gastric lesion is in danger and needs constant watching, perhaps immediate operation. Whether or not a gastric ulcer changes into a gastric cancer does not interest me much. I think it sometimes does, but I can seldom see it happening. The gastroscopists are probably going to show us more and more cases of this type because they are going to see the lesions in an early stage and are going to watch their metamorphoses as they never could be watched before. What I am sure of from much sad experience is that every time I see a patient with a gastric ulcer I must be worried about him, and I must keep worrying about him and watching him. Why? Because I have found that in an uncomfortably large percentage of cases after a gastric ulcer has been removed or apparently healed, back comes the patient with a carcinoma of the stomach. That is why we at the Mayo Clinic are always worried about people with gastric ulcer. We are particularly worried about the older man with a short history—so worried that often we explore his abodmen surgically, and often that is the only way in which we can save his life. More often we go in and find it is too late, the growth has scattered.

The next big problem to face is that of examining at yearly intervals the stomach of the man past middle age. I have an X-ray examination of my stomach made almost every year: I know that this is the only way in which I can perhaps save myself from dying with carcinoma of the stomach. I am sure of this after all I have seen in the last 30 years. And yet even now I am not taking sufficient care because once a year is probably not frequent enough for safety. I feel sure that in 6 months I could develop an inoperable carcinoma of the stomach.

If we are to get anywhere with the diagnosis of cancer of the stomach, we must first get doctors to change a curious point of view. Today when the average physi-

cian sees a lesion in the stomach that looks anywhere near like an ulcer, he says, "It is a benign ulcer," and you have to work on him a long time to get him even to consider the possibility that it might be carcinomatous. At the Mayo Clinic for years we have been looking at the problem the opposite way; we say that in an elder man with a "short history" and any lesion in the stomach, the chances are that it is malignant, and we must look on it as malignant until we can prove it is benign. Unfortunately, we are all still seeing too much carcinoma of the stomach that is inoperable, and I don't think there is much improvement in the situation during the last 15 years. As I showed some time ago, doctors who come in with carcinoma of the stomach generally have let things slide for about 12 months, whereas the layman comes in after about 11 months of neglect or treatment for "ulcer."

How much danger does the patient with gastric ulcer run? That we will try to find out with good follow-up studies. Insurance statistics that were gathered years ago showed that the man with gastric ulcer was not a good risk for an insurance company to take; a man who had had a duodenal ulcer appeared to be a good risk for an insurance company if he had gotten by long enough so as to greatly diminish his chances of getting a jejunal ulcer.

Here is a question that I think we ought to try to solve. Why do we not at necropsies find more small beginning cancers of the stomach? I have wondered about this. I see the important organs from somewhere around 600 autopsies a year, and I wonder why I see so few small plaques or nodules. We find any number of unexpected carcinomas that gave no symptoms during life, but most of them are large. All of you who perform autopsies know that. Now why is it? In the colon we often see polyps as forerunners of carcinoma, but I seldom see them as forerunners of carcinoma in the stomach.

SATURDAY AFTERNOON SESSION

OCTOBER 12, 1940

(Dr. James B. Murphy, Rockefeller Institute for Medical Research, presiding.)

Chairman Murphy: The next paper on the program will give you an idea of the plan back of this conference. The Council hoped not only to stimulate interest but to see a concrete plan evolved to attack the problem of gastric cancer. Dr. Voegtlin, the Chief of the National Cancer Institute, will discuss a program for the study of cancer of the stomach.

A Program for the Study of Cancer of the Stomach

By Carl Voegtlin, *chief, National Cancer Institute, National Institute of Health, United States Public Health Service*

Permit me first to express the appreciation of the staff of the National Cancer Institute and myself to all those who have taken an active part in this important conference on gastric cancer. We have learned a great deal, and we shall make full use of this information in our work.

My part is to discuss a possible program for the study of gastric cancer. The task is not an easy one, because no one individual is competent in all these various fields. All I can hope to accomplish is—first, to present, on the basis of the preceding discussions, certain definite questions which appear to be susceptible of investigation, and second, to integrate the various questions into a somewhat logical plan.

This afternoon's discussion also should serve to crystallize various problems so that they can be considered for financial support by foundations and by the National Advisory Cancer Council.

Let us first appraise the present effectiveness of gastric cancer control. There can be no question that the data presented by Mr. Collins on mortality rates and prevalence, as well as clinical experience, clearly show that gastric cancer for the country as a whole is a highly fatal disease, accounting in the year 1938 for 27,102 deaths.

The outlook for the future would indeed be a pessimistic one, were it not for the fact that this conference has opened up certain approaches, which, if pursued intelligently and persistently, are bound to make for a much better understanding, followed by a better control of gastric cancer.

STATISTICAL STUDIES

The statistical data on mortality rates and incidence should be continued and kept up to date in order to serve as a broad basis for the evaluation of the effectiveness of new control measures. This work is in progress in the Division of Public Health Methods. It seems also of interest to secure a possible explanation for the curious geographic distribution of gastric cancer mortality, with the high rate in the Northern and Northwestern States. A casual investigation of this problem would be a waste of time, but a carefully planned epidemiological study by competent investigators might very well bring out valuable information. For instance, it would be interesting to seek a correlation of the incidence of some of the suspected precancerous gastric lesions with gastric cancer, or a correlation of certain dietary factors and deficiency diseases with gastric cancer. The results of such studies would obviously not be conclusive in themselves, but they might offer suggestions for laboratory and clinical studies in somewhat the same way as epidemiological studies have contributed to a better understanding of the etiology of pellagra. Such work necessarily would require a minimum of 2 and probably more years in order to yield any statistically valid results. Dr. Crabtree has made a start on this problem.

CAUSATION OF GASTRIC CANCER

The discussions during this conference have confirmed my conclusion reached from a study of the literature, that there

is a lack of convincing evidence as to the causative factors responsible for the production of human gastric cancer. It is quite reasonable to consider certain chronic gastric pathological conditions, such as atrophic gastritis, benign gastric polyps, and perhaps gastric ulcer as precancerous conditions. But the proof for the correctness of such assumptions is still lacking. For this reason, the comprehensive studies of Dr. Reid and his colleagues on the relation of chronic atrophic gastritis to gastric cancer are of great importance. Dr. Reid has told us that it will take 10 to 15 years to secure the answer. I raise the question, therefore, whether it would not expedite the solution of this problem by having other competent clinics carry on this same line of investigation. This would have the advantage of securing statistically valid results much sooner. It is quite evident that a very large number of cases of chronic atrophic gastritis will have to be studied in order to arrive at a final answer. In order to think through this problem as to its eventual consequences, we must consider how the proof for chronic atrophic gastritis as a predisposing factor for gastric carcinoma would open up ways of controlling the latter disease. First, it would emphasize the need for frequent and thorough gastric examinations of all cases of atrophic gastritis in order to detect early gastric carcinomas. Second, as pointed out by Dr. Schindler, it would mean that prevention of chronic atrophic gastritis would make for better prevention of gastric carcinoma. In order to prevent chronic atrophic gastritis, we must know its etiology. Here is another important unsolved problem.

It would appear that careful dietary studies on cases with chronic atrophic gastritis, especially investigation of the *dietary habits preceding the disease*, may furnish useful information. It is recognized that this kind of work is apt to be full of pitfalls, as most persons have only a vague recollection of the kinds and quantities of food they consumed 2, 5, or 10 years previously. However, by selecting intelligent and cooperative patients, valuable information might well be secured. There is no doubt in my mind that such clinical investigations are very important.

Dr. Rhoads has presented interesting evidence on the possible etiologic relationship of pernicious anemia and gastric cancer. It is very important to secure further evidence in support of this view, though it may be questioned at this time whether a large proportion of gastric carcinomas are *caused* by a preexisting pernicious anemia. This work would naturally require many years of effort in order to arrive at a conclusive answer. A particularly significant feature of this research as pointed out by Dr. Rhoads, is the relationship of a special type of atrophic gastritis to a specific dietary factor—the liver factor of pernicious anemia.

A further possible relation between pernicious anemia and gastric cancer was brought out by the interesting observations of Dr. Brunschwig on the occurrence in both diseases of a factor in the gastric secretion and in gastric tissue which, when injected intravenously into dogs with gastric pouches, inhibits the secretion of hydrochloric acid. It is important to pursue this research from several points of view: (1) To obtain information on the chemical character of this factor with a view to its ultimate chemical isolation; (2) since achlorhydria is a common feature of both pernicious anemia and to a lesser degree of gastric carcinoma, it would be interesting to subject suitable experimental animals to long-continued parenteral injections of the inhibiting factor in concentrated and purified form, with a view to

determining whether this treatment would cause gastritis and perhaps gastric cancer; and (3) to explain the failure to demonstrate the presence of the inhibiting factor in *all* cases of the two diseases.

A real effort should be made to utilize the wealth of clinical material available in well-organized clinics for such systematic studies on causation of gastric cancer. Consideration might very well be given to a proper coordination of such investigations carried on in a few well-selected clinics. The time has arrived when at least as much consideration should be given to the etiologic study of gastric cancer in medical schools and hospitals as has been devoted in the past to the study of many less important diseases. There is reason for optimism that this will be done, if for no other reason than the presence at this conference of many leading clinical investigators.

The next question is: What can experimentation on animals contribute to the etiology of gastric cancer? First, new knowledge concerning the physiology of the stomach, as illustrated by the recent work on the function of enterogastrone and urogastrone, is likely to be of value as a physiological basis for the ultimate explanation of a pathological process, such as chronic atrophic gastritis or gastric carcinoma. While this certainly deserves mention, it does not come quite within the scope of this conference. All cancer research has a broad biological aspect and in order to limit its scope, it is necessary to leave the purely physiological part to physiologists. Second, the experimental production of any disease under well-defined conditions is generally considered as an important contribution to the study of disease. As concerns gastric cancer, Dr. Stewart's presentation and the discussion following have shown that a good beginning has been made. Squamous-cell carcinoma of the forestomach in certain strains of mice has been produced, which fulfills all the requirements of a truly malignant tumor. The production of gastric squamous-cell carcinoma by Lorenz and Stewart furnishes a basis for further work on the histogenesis and other interesting aspects of this tumor. Further work will have to be done to ascertain whether genetic constitution plays a role. There are also definite indications that the nature of the medium used for the administration of carcinogenic hydrocarbons is a factor in tumor production. This may determine intimate contact with, and absorption of the carcinogen by the gastric mucosa.

The interesting adenomatous lesion in mice of strain I suggests that at least in these animals hypertrophic gastritis as such does not predispose to gastric cancer. However, further work is indicated, to ascertain if under certain dietary regimes this hypertrophic lesion will give rise to malignant glandular lesions.

A point which deserves to be emphasized again is the relatively low susceptibility of the gastric glandular tissue in the mouse to tumor formation, following direct injection of highly potent hydrocarbons. This, in conjunction with the rarity of spontaneous gastric cancer in the lower animals, suggests that attempts to produce experimental cancer should be so designed as to keep animals under observation for a year or much longer, depending on the species of animals selected for the purpose.

The important problem now to be solved is the production, by means of carcinogenic hydrocarbons, of gastric adenocarcinoma in suitable experimental animals. Work along this line is in progress at the National Cancer Institute. Even of greater importance would be the experimental production of this disease by conditions suspected as being concerned in the causation of human gastric carcinoma. Dr. Stewart has

referred to Roffo's work on the production of gastric carcinoma in rats following the feeding of cholesterol and foods irradiated by ultraviolet light or of heated fats. Roffo's claims are open to criticism. Yet it would appear that a careful and systematic investigation of the possibilities of producing gastric cancer in animals subjected to certain dietary regimes for long periods is worthy of attention. Early last spring work along this line was begun under my guidance by Doctors Larsen, Morris, and Lippincott. This is considered as a major research problem of the National Cancer Institute and will be pursued intensively. The object is to reexamine Roffo's work on the production of gastric tumors by heated fats and also to broaden the scope by inclusion of other dietary factors as possible causative agents of gastric lesions and gastric tumors. I believe that such studies on rats and other animal species, particularly dogs, if correlated with the above-mentioned projected clinical investigation on dietary factors, represents a promising field well adapted for the collaborative work of the Institute.

In view of what has been said about the lack of information concerning the causative factors of chronic atrophic gastritis in man, attempts to produce this condition in experimental animals are called for. The literature contains a few rather unsatisfactory reports on the experimental production of this disease as the result of the chronic administration of alcohol and other drugs and poisons. Here again, emphasis should be placed on conditions which presumably operate in the production of atrophic gastritis in man. Should it be possible to produce experimental chronic gastritis, the way would be open to determine if gastric cancer does arise as a consequence of this condition.

What role, if any, abnormalities of nervous innervation of the stomach, hormones, or infectious diseases may play in the causation of gastric cancer is an open question. All that can be said at present is that there are no definite indications of the operation of such factors. At all events it is wise not to overemphasize the importance of extrinsic (dietary) factors, but to give consideration to intrinsic factors as well.

DIAGNOSIS

There is general agreement that a correct diagnosis of more or less advanced cancer of the stomach can be made in the great majority of such cases by repeated X-ray examination in combination with functional tests. Dr. Schindler, Dr. Reid, and others have advocated the use of the gastroscope in combination with other diagnostic methods. Gastroscopic biopsy has been mentioned as a possibility. There seems to be considerable promise that the wider use of the gastroscope may improve the accuracy of the diagnosis of gastric cancer with particular reference to the recognition of "early" cancerous lesions in patients who have no specific clinical signs and who are examined gastroscopically for suspected gastric pathologies.

Dr. Schindler's recommendations for the training of highly qualified roentgenologists and gastroscopists is a proper function of medical schools and hospitals and requires only endorsement by this conference, if this is the consensus of opinion.

There is need for some action with regard to Dr. Schindler's recommendation for classification of gastric tumors for the purpose of prognosis. The question is before the conference whether a central bureau (gastric cancer registry) should be established for the purpose of collecting gross specimens, microscopic slides, and statistics about follow-ups. After further dis-

cussion it may be desirable to refer this aspect of gastric cancer research to a small committee for the formulation of concrete plans to be submitted for consideration for support to the National Advisory Cancer Council and to private foundations. The main difficulty would be assured financial support for a period of several years. Consideration might be given to the American College of Surgeons, the American Association of Pathologists and Bacteriologists, and the roentgenologists taking part in such a project. This voluntary collaboration would considerably reduce the expense involved.

TREATMENT

For the sake of completeness, brief reference is made to possibilities of improving the treatment of gastric carcinoma. At present this, of course, is a surgical problem. X-rays offer relatively little hope. In all likelihood neutron therapy, when tried, will have essentially the same limitations as those pertaining to X-rays. However, there is the theoretical possibility that some time in the future a chemical may be discovered with sufficiently specific action on the cancerous tissue to arrest tumor growth or to cause complete regression. Emphasis, therefore, should be put at this time on improving the chances of early diagnosis.

As lay education plays a part in effective treatment, it may be desirable for this conference to pass a suitable resolution endorsing the efforts in this line of the American Society for the Control of Cancer, of the State health departments and cancer commissions, and of the National Cancer Institute.

CONCLUSION

In conclusion you will agree that the conference has clarified the whole gastric cancer problem as has never been done before, that it has suggested certain important lines of investigation, and that it has dispelled to a considerable degree the previous pessimism surrounding this problem. After all, constructive thinking and work are the first requisites for the solution of any scientific problem, whether the problem is complex or simple.

Dr. Voegtlin: I should like to say only one more thing. Are you sufficiently interested in these proceedings to have the National Cancer Institute publish them?

(The sentiment for publication was practically unanimous.)

DISCUSSION

Chairman Murphy: Dr. Shields Warren will open the discussion.

Dr. Warren: Dr. Voegtlin has so well summarized and recalled to our attention the worth while points of the conference that there is but little for me to add. I should like, however, to pick out a few points for more particular emphasis. One valuable form of statistical material that is not utilized nearly as much as it should be in this country is the material that may be obtained from the various coroners and medical examiners. People, presumably in health, are killed by automobiles or other means in appalling numbers, and so far but little effort has been made to have routine autopsies done and find out what we can about the early stages of various disease processes. In a disease like gastric cancer that is so rarely seen early, I think that point is of special importance.

In Dr. Collins' study I think it would be interesting to add to the general mortality statistics the autopsy findings as a separate, more accurate type of statistics, from various key cities in different parts of the country. These are represented, to be sure, in the death certificates, but are not

separately given in the census returns, so far as I know.

In this difference that exists between the findings of gastric cancer in the North and in the South, there may well be some racial variations as well, just as the strain I mice are more prone to have lesions in their stomachs than are other strains. There seem to be some trends, judged by the statistical studies that Dr. Herbert Lombard made in Massachusetts, that certain of the foreign-born may vary as contrasted with native-born in the frequency of gastric cancer.

As a pathologist I was particularly interested in the problem of classification of gastric tumors. Borrmann's classification, as outlined by Dr. Schindler, is a most satisfactory one. The microscopic classification, however, is important to follow as well. At present, it is impossible to get any satisfactory correlation between group or individual prognosis and microscopic appearance of the tumor. I think this is probably due to the rather uniformly bad results in most cases of gastric cancer, and I should like to see a third type of classification introduced parallel to that used in the cervix, in the breast, and other lesions, where the extent of the disease is brought in; whether it involves a portion of the stomach, all the stomach, or the regional nodes when first seen. At autopsy in cases of carcinoma of the stomach, I have been impressed by the fact that half of our cases were operable in the ordinary sense, aside from the condition of the patient, in that the disease in over half of these autopsy cases was restricted to the stomach and to the regional lymph nodes. Distant metastasis, even at autopsy, is not present in half of the cases.

I think one other point that must be kept in mind—it was hinted at by various speakers—is that carcinoma is not the only lesion of the stomach. Solitary lymphomas are quite readily amenable to treatment, and also the leiomyosarcomas and some of the nerve tumors and fibrous tissue tumors, though presenting very formidable appearances, may be sufficiently localized to be amenable to therapy.

Very few of the clinics can hope to have as fine a unit for study as that outlined by Dr. Reid. Fortunately, however, adding one or two interested men, primarily giving their time to gastric cancer, to various active units, should do a great deal to develop our knowledge of the disease. There are in many general hospitals and general clinics large masses of material at hand which simply need coordination and interest in order to add to our mass of already available information. While the ideal situation would be to have every large medical center equipped with such a unit as Dr. Reid's, I think that possibly less elaborate units scattered through the country would be of very material assistance.

From the experimental standpoint there is one thing that has interested me particularly. There is in the stomach of the rat and the mouse a rather different physiologic set-up from that in the human, and I should be interested in seeing such studies as Dr. Stewart and his coworkers have been carrying on extended to animals such as the dog, the cat, and even to the primates, so that we might have data more nearly comparable with the conditions found anatomically and histologically in the human.

From the standpoint of gastritis, which is our most hopeful point of attack, some of Dr. Stewart's observations were particularly interesting, in that in the lesions produced by carcinogens, changes have been produced in the submucosa and in the muscularis which definitely would interfere with the nutrition of the overlying epithelial tissue. This I feel deserves further investigation.

Chairman Murphy: I will ask Dr. George Holmes to speak.

Dr. Holmes: I wish to apologize for interrupting the symposium this afternoon. As you will remember, a general discussion was not possible on the papers of Dr. Schindler and Dr. Reid, and it is in regard to these papers that I will speak. Since the radiological examination is recognized as one of the most important factors in the early diagnosis of cancer of the stomach, it would seem to me that a word from the radiologists on that subject should be of interest to you.

First, in no branch of radiology has there been such progress in recent years as in the examination of the gastrointestinal tract. The introduction of the study of the mucosal relief which Dr. Schindler referred to is a most important addition to our armamentarium, and one which is not generally used throughout the country. The technique is quite difficult, and the interpretation is even more difficult. It requires considerable study and experience to carry out this type of examination satisfactorily.

I could not help being unfavorably impressed with some cases that were shown at this meeting. I must say that I felt that this new method had not been used, otherwise some of these lesions would have been demonstrated.

Any method which carries a high percentage of accuracy in gastrointestinal examination, 90 percent or over in expert hands, also carries with it a considerable responsibility. The patient and the referring physician feel that if the X-ray examination is negative they are fairly safe and this may not be true. I was pleased to hear Dr. Reid state that a positive examination is of great value, and that a negative examination may be of no value. I was a little disappointed to hear in this meeting the expressions, "what the X-ray shows" or "what the gastroscope shows." I think we should say what the examination shows or what the gastroscopist or roentgenologist finds. In other words, let us not emphasize too much the machine, but let us get back a little more to the man who is handling it.

It is true that a large amount of X-ray work is being done throughout this country by men who are not sufficiently well trained. That is not their fault. It is because of the increasing demand for this kind of work and because of the inability of the teaching centers to train men fast enough. A set-up is now available which will turn out much better trained men, and I expect there will be a very definite improvement in the near future.

There are some conditions which lead to an early diagnosis at a time when the patient is curable. One of these is the condition of the patient who comes in with bleeding. No patient with bleeding from the gastrointestinal tract should be discharged lightly, even though the X-ray examination is negative. Frequently a negative X-ray examination becomes positive when conducted by a man of greater experience.

Another condition which has interested me is the so-called malignant ulcer. I agree with the speakers that the radiologist is usually not in a position to decide whether a given ulceration is malignant or benign. In these cases the gastroscopist is of the greatest help. At the Massachusetts General Hospital for some few years, we have been advising surgical removal of all gastric ulcers situated within 1 cm. of the pylorus, and I should like to call your attention to the fact that ulcers in certain parts of the stomach, even though they appear to be benign, are likely to be malignant. Most gastroenterologists recognize that an ulceration in the cardiac end of the stomach or on

the greater curvature of the stomach is potentially malignant. I should like to add any ulceration in the prepyloric region.

The cost of X-ray examination has been emphasized. I think clinicians as a whole have a feeling that it is altogether too costly a procedure. There are certain factors that do make the cost high. One is the constant improvement of apparatus. Radiologists are perhaps more dependent on their tools than any other group of men, and unless they have the best tools to work with it is impossible for them to do the best work. A modern set-up for gastrointestinal examination with the various special devices costs in the neighborhood of $8,000, and it may be out of date in 5 years. In the 30 years in which I have had charge of the roentgen department at the Massachusetts General Hospital, we have changed our equipment every 5 years; but taking all these things into consideration, cost to the patient is only $5.00.

In private practice it is true that a man has to collect a larger fee, but I don't think that even this is much of a stumbling block.

I was interested in what Dr. Ewing said about the sensitivity of tumors in relation to gastric cancer, and regarding the question of therapy in gastric cancer. I think that as a general rule any cancer that can be safely removed surgically is better treated that way, but radiation has a large palliative field, and certain types of cancer which grow outward from the body surface are much more likely to be affected favorably by radiation than cancers which are infiltrating.

There are certain cancers of the stomach which arise in the fundus and which appear as large cauliflower-like masses and are in a position where operation is particularly dangerous. Some of these cases I think should receive radiation treatment under careful management.

Chairman Murphy: Dr. Morton will discuss the subject.

Dr. Morton: When Dr. George Smith told me there would be a conference here and asked me if I could give him some methods by which clinical material could be studied in a more comprehensive manner, I drew up an outline on cancer material of the stomach indicating how it might be investigated. It should have a broad general approach, because we have very little to contribute to it in a clinical way, and I think really a mass attack should be made on the subject.

The large medical schools and medical centers have on their faculties men who have the medical talent necessary to work out any new facts that might be uncovered in such an appraisal of this disease.

In a place like the University of Rochester, we have had available for the last 3 years roughly 40 to 50 cases of cancer of the stomach a year. That would seem to be adequate material, assuming that only a third of these cases would be suitable for study. The ordinary clinical studies should be made, as they are now, including all the special laboratory tests. In addition to gastroscopic and roentgenologic studies, I think a group of beds should be set aside where these patients could be intensively studied.

In the medical service, as in our institution, we have men who are trained to do the mineral metabolism of patients. That is under Dr. McCann. We have metabolism equipment used for that purpose, and there are men there who have studied these factors for other diseases.

Dr. John Murlin, in physiology, is very much interested in gastric secretions and has men in his department who contribute to this field. Dr. Nassett, for instance, has brought out one or two of the new

enzymes in the upper gastrointestinal tract. This department would be prepared to make a study on the enzymes and the secretions of patients with this disease.

Of course, we do not know whether the estrogens have anything to do with carcinoma of the stomach or not, but if they do by any chance, we have men who are qualified to estimate both the estrogens and the androgens.

On the question of deficiency states: In Dr. George Whipple's laboratories we have animals with controlled deficiencies in the blood-cell volume, hemoglobin, and plasma volume. These animals could be used for a study of primary and secondary anemia factors and for plasma-volume factors.

In the surgical laboratories, Dr. Mahoney has already found a disturbance in the plasma-protein ratio in some forms of gastrointestinal cancer. It might be that this should be investigated much more thoroughly and that determinations of the distributions of the proteins in the plasma should be made. The Tiselius apparatus would be an ideal thing to have. We do not have one. Dr. Bayne-Jones told me that at Yale they have one, and he has offered to carry on any such studies which we might wish to make.

There are 35 or more people who are at work now on radioactivity at the University of Rochester. They are all in different departments. It would be relatively simple to study the appearance with a Geiger counter of various ions and radioactive substances introduced into patients with gastric cancer. For instance, in experimental animals, the appearance of a radioactive substance has been found in the serum from an isolated pouch in a very few minutes after its introduction.

In the department of pediatrics, Dr. Clausen has been interested in the vitamin distribution in children. He is qualified to study that phase of the subject.

The health bureau is in close association with the University of Rochester, and it would be possible through it to make a good survey of geographical locations, social status, eating habits, epidemiology, etc., concerning the problem.

Of course, the surgical department has the problem of therapy, where the main mortality results from hypoventilation of the chest following surgery. There is post-operative pneumonia, as a great risk in these operations.

There are other questions which might be decided by pathological sections, such as Dr. Reid showed this morning. From the surgical standpoint, it is important to know how far the resection should go into the duodenum. I have always considered that the duodenum is relatively immune to the extension of cancer and one should have a fair margin of safety. But one or two resections that I had an opportunity to follow years later seemed to have recurred on the duodenal side. There is some evidence from the Massachusetts General Hospital series that invasion of the duodenum may occur. I wonder if questions such as that might be answered by Dr. Reid's material. I am glad that Dr. Holmes spoke about the radiologist in connection with this problem, because he is one man to whom I owe a great deal for interest in this problem. When I was resident surgeon I spent practically one or two afternoons a week with him, running through gastric cases. I believe that every surgeon would be much better off if he could see the radiologist work out these difficult diagnoses.

Chairman Murphy: Dr. Oughterson will discuss the paper.

Dr. Oughterson: Dr. Murphy, and Members of the Conference: This conference has been so well organized and executed

that at this time there is very little left for me to say. However, as a surgeon whose major interest is in cancer, I should like to make a few remarks, and with your permission I should like to show some lantern slides.

Dr. Dochez this morning emphasized the fact that internists have not been giving as much attention to the cancer problem as the problem deserves. I thought that in relation to this it would be interesting to show the results of a study of cancer of the stomach in the city of New Haven (fig. 1). Most cancer studies are based on the material found in certain institutions, and there is comparatively little information based upon the total number of cancer patients found in a community. It is frequently assumed that cancer of the stomach is chiefly a surgical problem, whereas it may be seen in figure 1 that more than 90 percent of the problem is a medical responsibility. Late diagnosis and operative mortality are the two chief factors which limit the surgical curability of gastric cancer. The operative mortality for gastric cancer in this country is unknown. There are large cities where the average operative mortality is 50 to 60 percent. The best clinics have shown that an operative mortality of 10 to 15 percent may be achieved. This compares favorably with the operative mortality for acute appendicitis in the same age group. It is probably fair to state that the average operative mortality for gastric resections for cancer is close to 35 percent. However, even if there were no operative mortality, 90 percent of the problem of gastric cancer, from the therapeutic standpoint, is one of medical diagnosis.

Some better and simpler means of

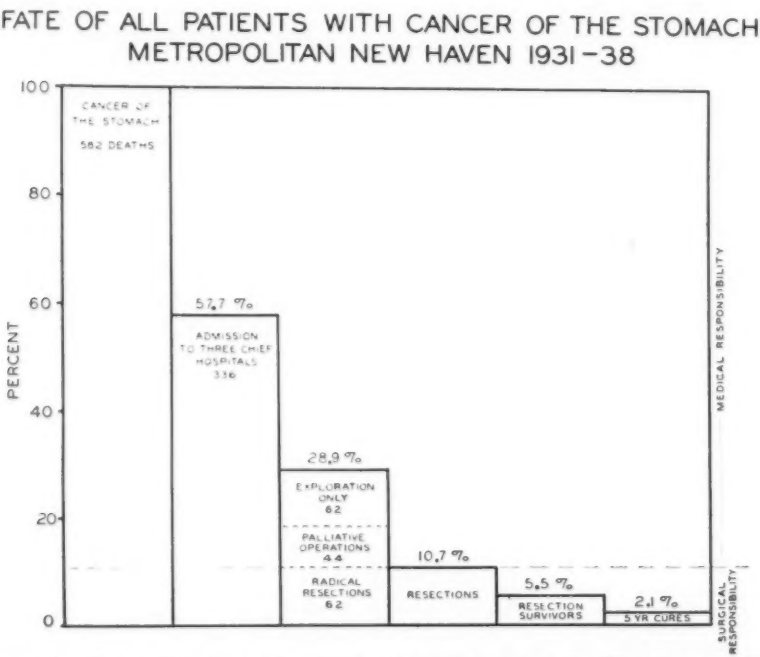

FIGURE 1.—Fate of all patients with cancer of the stomach, metropolitan New Haven, 1931–38.

diagnosis is one of our greatest needs in order that the therapy of gastric cancer may be improved. Departments of medicine should assume a greater responsibility for investigations along these lines.

The delay in diagnosis of gastric cancer has received considerable attention, but as yet no considerable progress has been made in remedying this situation. The responsibility for the late diagnosis is shared equally by the public and the physician. The education of the public is a responsibility which has been assumed by the American Society for Cancer Control as well as the various State societies. The education of the physician is fully as important and must be attained through the State medical societies and tumor clinics with a far more intensive program than we have had to date.

Late diagnosis using our present methods can never be entirely eliminated. However, as figure 2 indicates, there are great but as yet unrealized possibilities in this direction. The period of delay (fig. 2), taken as 3 months, is undoubtedly far too long; 1 month is sufficient for a patient to have symptoms before having diagnostic investigations carried out. However, with 3 months as the standard, there are nearly 40 percent of the cases in which the major responsibility rests on the physician. The error chiefly responsible for delay is failure to take advantage of modern diagnostic methods. It is possible that the lack of such facilities or the expense entailed may be important factors in this delay. However, these facts may be readily determined by investigation.

The surgical curability of early gastric cancer is encouraging, as has been mentioned by Dr. Alvarez, and is illustrated in figure 3. The curability of early gastric cancer has been obscured owing to the fact that such a small percentage of cases are diagnosed early. In early operable

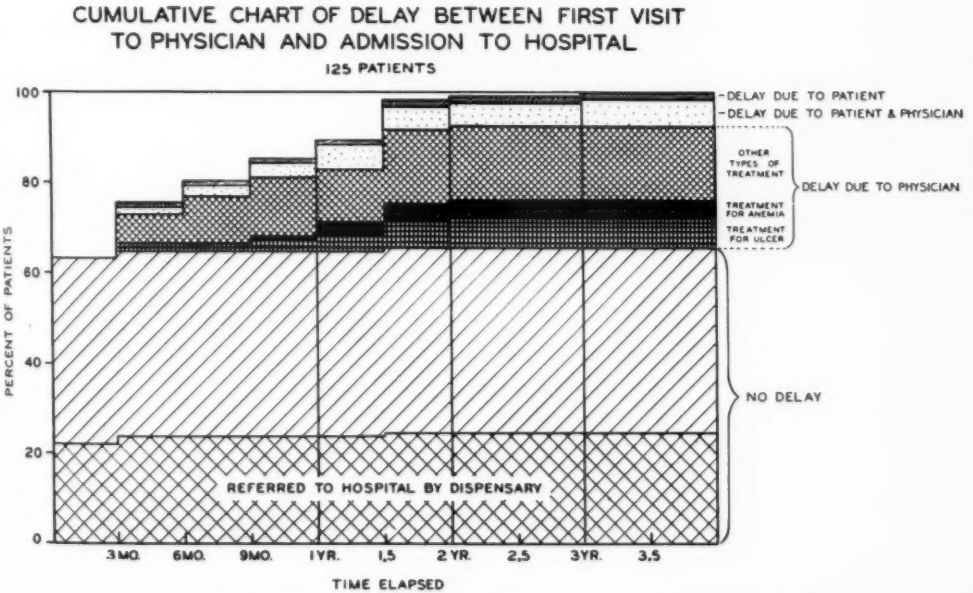

FIGURE 2.—Cumulative chart of delay between first visit and admission to hospital.

cases approximately 50 percent 5-year cures are obtained.

The value of gastric analysis in the diagnosis of cancer of the stomach has

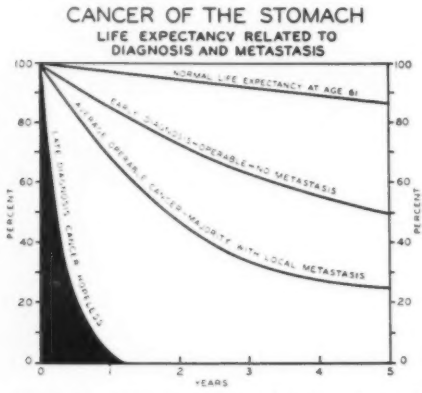
CANCER OF THE STOMACH
LIFE EXPECTANCY RELATED TO DIAGNOSIS AND METASTASIS
NORMAL LIFE EXPECTANCY AT AGE 61
EARLY DIAGNOSIS-OPERABLE-NO METASTASIS
AVERAGE OPERABLE CASES-MAJORITY WITH LOCAL METASTASIS
LATE DIAGNOSIS CANCER HOPELESS
PERCENT
YEARS

FIGURE 3.—Life expectancy related to diagnosis and metastasis in cancer of the stomach.

for some years been a controversial question. As an isolated finding it is of questionable value, but in conjunction with other data it is of great value. It should be mentioned that the so-called normals in figure 4, with a low or absent acid, have a far greater chance of later developing a cancer of the stomach than if the acid were normal or high. Chronic gastritis or a precancerous lesion was discussed this morning, and in this relation there is one factor which I hesitate to mention because it is the old bugbear of chronic irritation and infection.

Patients with a low gastric acidity, with or without cancer, have a greatly altered bacterial flora in the stomach. In some patients we have found this comparable to the bacterial flora of the large intestine, and they may require a continuous drip of N/10 hydrochloric acid for a week before the stomach is sterilized. This infection is undoubtedly secondary to the altered physiology and is not the sole cause of chronic gastritis. However, it is not clear how large a role it may play. There are comparatively few data relative to altered gastric secretion in cancer of the stomach other than those relating to acid secretion. Further investigation of this field might prove fruitful.

The etiological factors in cancer of the gastrointestinal tract are still obscure. It is also not known whether factors causing cancer in one portion of the gastrointestinal tract may cause a similar lesion in another portion.

Studies on the incidence of cancer in various parts of the country, as pointed out by Dr. Voegtlin, may yield valuable clues which can be verified in the laboratory. In a similar manner the incidence of cancer in various parts of the body under certain circumstances may yield leads as to possible etiological factors.

Table 1 shows the incidence of cancer in various parts of the body as related to

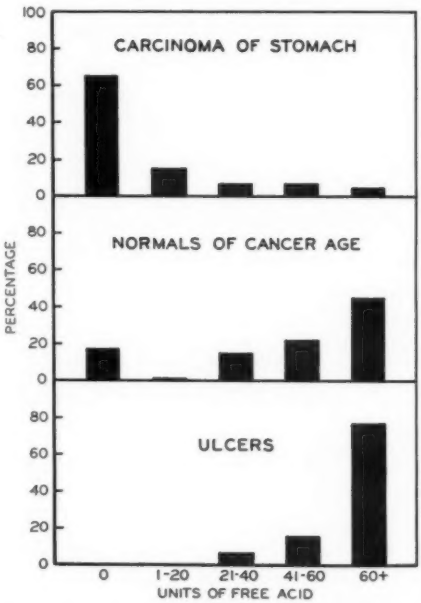

FIGURE 4.—Gastric analysis: Frequency distribution of free acid values after histamine.

the ratio of male to female and of ward to private patients. In the lip and oral cavity the high ratio in the male as compared with the female is impressive. A similar but less striking ratio is found between ward and private patients. It may be worthy of note that in the breast, where cancer is thought to be caused by internal rather than external factors, the ratio is normal.

TABLE 1.—*Cancer incidence in 860 patients at New Haven Hospital, 1935–39*

Site of cancer	Cancer-incidence ratio of—	
	Male to female	Ward to private patient
Lip	48.0:1	4.4:1
Oral cavity	8.0:1	5.8:1
Esophagus	6.3:1	6.3:1
Stomach	2.1:1	6.0:1
Colon	1.0:1	2.0:1
Rectum	1.8:1	2.5:1
Skin	2.2:1	1.4:1
Larynx	6.5:1	2.0:1
Lung	5.5:1	6.2:1
Breast		1.1:1
Total admissions over age 35	1.0:1	1.0:1

Such studies suggest that cancer of the gastrointestinal tract may be influenced by external factors, which are more common in the male and in those of a lower economic status, and are more effective in the upper portion of the gastrointestinal tract. We have not as yet attempted to determine the possible factors involved. However, it would seem that planned studies carried on in widely differing geographic areas on a larger scale might yield further clues as to the etiology of gastric cancer.

Chairman Murphy: Dr. Winternitz, will you participate in the discussion?

Dr. Winternitz: I am glad indeed to have the opportunity to thank all of you responsible for this conference for the privilege of being allowed to attend. It has been illuminating and interesting. May I stress one or two points. Firstly, may there not be danger in the development of highly specialized groups for the study of gastric cancer unless the fact is borne clearly in mind that the local disease is only an ultimate expression of more profound and more general disturbances in physiology?

It is obvious that consideration of etiological factors would include in the first category local irritants, especially if they have undesirable social associations. I am inclined to believe this approach is relatively unimportant.

Atrophic gastritis as a forerunner of cancer of the stomach has been stressed quite properly. Its relation to pernicious anemia and sclerosing processes in the central nervous system associated with this syndrome is outstanding evidence of the relation of local manifestations of disease to the more fundamental and general functional changes. The contributions of Dr. Rhoads and others, especially Dr. Brunschwig, reported here, have emphasized this phase of gastric cancer in its relation to chronic atrophic gastritis. Little is known of the latter condition. The name rather implies that it results from long-continued irritation of the mucosa by hot or cold, highly seasoned food, alcohol, and like agents. May it not be an expression of lack of functional stimulation through some essential agent arising in some other and remote organ of the body?

I am inclined to believe that in the study of chronic diseases ultimate etiological factors may be far removed and that difficulties arise, as they do in malignancy, when the local conditions are overstressed. Pernicious anemia bears this out. Whipple's important contributions to the cause of this disease, of insidious onset and chronic course, no doubt were aided greatly by his development of a standard anemic dog for testing. Such an animal, with reduced factors of safety,

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provides opportunity not available in the more responsive normal organism. Obviously there are many ways of reducing factors of safety. Then acute processes may result quite different in extent and in location from what may have been anticipated.

This has been our experience with tissue extracts, used with normal animals and others whose factors of safety have been altered. Such extracts are, of course, very complex mixtures of chemical agents—agents that must be cared for by the body in the breakdown associated with the natural life cycle of each cell system. This process varies in extent and speed with individuals at different age periods and as a manifestation of many varieties of stimulation and disease. Injection of extracts or fractions of organ extracts in normal as well as in animals with decreased elimination offers an approach that has been utilized extensively with ductless glands but only to a minor extent with other organs and tissues. Lesions result which could not have been anticipated, but they are difficult to interpret because the extracts represent very complex chemical mixtures. In the light of present knowledge, it would be an assumption to include growth-promoting substances in these organ extracts. To exclude the possibility would seem to be even a greater error. Atypical as well as normal growth, in the last analysis, must be considered as chemical processes, and overemphasis of chemistry of the cell in relation to growth would seem to be out of the question at present. It is not only important to know whether there are chemical agents within the cell that stimulate growth of cells of the same kind. It is equally desirable to ascertain the chemical influences of all of the other organs upon the life cycle of any given cell.

Chairman Murphy: This concludes our formal program. The meeting is now open for general discussion and suggestions as to possible actions which may be recommended by the group.

Dr. Voegtlin: Mr. Chairman, I have prepared a list of problems. Is it possible today to take some action on these problems, or on some of them? Perhaps you are not ready for action. I suggest, for the clinical studies, that a small committee be organized to consider this question very carefully and to formulate a concrete, sound program.

What is the pleasure of the conference, for instance, on future statistical studies on mortality, incidence, geographic distribution? Is that a desirable thing to carry forward in a modified form, an improved form?

List of Problems for Discussion and Action By the Conference

1. Statistical studies on mortality, incidence, geographic distribution.
2. Epidemiological studies.
3. Clinical studies on causation.
   a. Relation of atrophic gastritis to gastric cancer.
   b. Relation of pernicious anemia to gastric cancer.
   c. Further study of the factor inhibiting gastric secretion of hydrochloric acid.
4. Laboratory studies on causation.
   a. Production and study of gastric adenocarcinoma induced by carcinogenic hydrocarbons.
   b. Production of nonmalignant and malignant gastric lesions by dietary factors.
5. Studies on improvements of diagnostic procedures.
   a. Training of competent radiologists and gastroscopists.
   b. Further work on the gastroscope as a diagnostic instrument.
   c. Central diagnostic bureau.
6. Organization of a coordinated clinical gastric cancer service.
7. Education of the laity.

Dr. Macklin: Dr. Warren had an inspiration when he suggested using coroner's material to study the incidence of diseases, such as gastric cancer, in persons who have been in apparent health up to the time of death. It might be easier to get the required data on them than to make a study on government employes, as I suggested yesterday. The coroner's material, however, would lack the advantage of having data as to habits, etc., before death, and of the long period of observation during life that would characterize the material gathered from government employes. The difficulty with the usual approach to a problem of this type is that we study only the persons who have died of the disease under observation, and hence lack the control data which would be acquired from a study of a population some of whom have not yet developed and may never develop the disease.

We often make the mistake in statistical studies of assuming that because two different factors are running parallel in their behavior one is dependent upon the other. For example, I recall a brilliant exposition of the idea that drinking milk was the cause for all cancer. The article showed that in those countries in which milk consumption was high, the cancer death rate was high; where little milk was consumed, there the cancer death rate was low. The two figures, that for milk consumption per capita and the cancer death rate per 100,000 rose and fell together, and the conclusion seemed justified that one was the cause of the other. But the author of the article and the persons who read it forgot that both these factors were dependent upon a third common factor, namely, advances made by civilization. In civilized countries, preventive medicine is eliminating infectious diseases as a cause of death; and as we all have to die of something, we die of the constitutional diseases that have not been eliminated; and among these is cancer. In civilized countries, nutrition experts advocate the drinking of milk in large quantities. It is no wonder that the two figures run parallel. One would find that the use of telephones, or the driving of automobiles caused cancer in exactly the same way as the writer of the articles had found that milk caused cancer. In civilized countries, where persons are kept alive long enough to die of cancer, the number of telephones and the number of cars per capita are also high, but we would not claim that talking through a telephone causes cancer. The proper use of control material would eliminate these fallacies in statistical reasoning.

Diet as a cause of cancer has been mentioned or hinted at by some workers. There is a village in Norway where the diet is largely fish, in which 84 percent of the cancers are said to be gastric. Investigations of other communities in which fish is the main article of diet, such as Labrador, the Esquimos, etc., might lead to either a confirmation or denial of this idea. Questions as to the religious denomination of the patients with gastric cancer might be of interest, since Catholics probably eat more fish than do Protestants. Peculiarities of diet as related to the incidence of gastric cancer might be studied in many communities.

Why should we not have a committee made up of gastroenterologists, internists, surgeons, geneticists, etc., who would survey the field, and determine what are the things we should like to know about the patients with gastric cancer, if we are to arrive at any knowledge of the cause of this disease. In such large centers as the Memorial Hospital in New York, the Mayo Clinic, etc., there could be workers whose business it was to obtain the answers to this standardized list of questions. I say a special worker, because the practi-

tioner is interested in obtaining the type of information which will assist him in making a correct diagnosis, and even if he had the time or the interest to ask all the other questions, at present he does not know just what questions are the important ones to ask. If this were done, we could soon have a body of uniform evidence, on a group of patients sufficiently large to be of value. In our present method, each worker asks for information which interests him, and each worker sees for the most part too few cases to be statistically valuable. Then, such workers could do what is most important, gather data from a control population of the same age and sex distribution that was not suffering from gastric cancer. The same data exactly would be obtained from the gastric cancer group and the control group. With these two sets of data, we might arrive at some worth while facts.

A second suggestion of Dr. Warren is one which I heartily endorse. It is that the collection of data on cancer should be so carried out, that those deaths which are attributed to cancer and in which the diagnosis has not been confirmed by autopsy, be separated from those in which autopsy was carried out. I would add to that, not only those in which autopsy was done, but those in which a histological diagnosis by a competent pathologist was done at any time, either on biopsy material or on material removed at operation, but in which death was not followed by autopsy. We might then be able better to assess such data as we have, and judge whether the cancer death rate is low because few of the persons who died in that community were autopsied, while in another community cancer death rates were high because autopsy disclosed many cancers. It is essential, before widely differing death rates be accepted as indicating valid differences, that we know the reliability of the data on which the death rates were based.

Chairman Murphy: Is there any further comment or suggestion on the first one of these items?

Dr. Dochez: It would be of great advantage if men who are experienced in the study of cancer and who consider important certain factors that may be evident in the precancer phase of the disease, such as atrophic gastritis, would get together some detailed presentation of such factors and distribute them. Then we in the general hospitals would try to promote the collection of knowledge concerning these factors by all those who work in the clinic. Such data could easily be collected in general hospitals where interns are skillful and are well-trained nowadays in the collection of such data. The chief difficulty at the present time is that interns do not know what special kind of information is important in connection with certain diseases. For instance, in gastric cancer a general history is taken and a few questions are asked, but what particular questions to ask and on what particular factors to put emphasis remain unknown. If some sort of general outline could be drawn up laying emphasis on factors that are considered important, the information secured in general hospitals concerning these factors would be useful.

Dr. Little: Recognizing my complete absence of clinical knowledge, and with apologies for that, I have perhaps one or two suggestions to make along the line that Dr. Dochez has just spoken of. I hope they may be of a little value in discussing the different topics that Dr. Voegtlin's list contains.

As I see it, one of the things that is absolutely essential to the advancement of the problem is to increase our supply of available gastric cancer that can be studied

under conditions which we can as nearly as possible control.

The second thing, it seems to me, is that we can afford to focus on two points of view: (1) To study the history of the individual, the natural history, the life history, of the stomach, that is to say, the same stomach at different ages; and (2) to study the variations that occur within stomachs at the same age. These are two different points of view which are essential. One is to know what any one stomach can do throughout life, and the other is to know what all kinds of stomachs can do at any one comparable stage of development. In the collection of your histories in the hospitals I think those two points might be helpful.

There is one other thing that is an example, I guess, of where fools rush in where angels fear to tread, but I cannot get away from the fact that there seems to be a missing factor in the etiology of stomach cancer that we must look for somewhere. As a general thing, cancer occurs in organ systems or tissues where imbalance exists, where great activity is present, often cyclical, and where lack of control of these cycles is a reasonable thing to expect. Why doesn't man have more tumors of the brain? Theoretically, all the painful course of evolution has worked toward the development of our nervous system. There are great crises in it, and in civilization greater ones than in primitive conditions, yet the incidence of cancer in the human nervous system is not among the highest compared with other locations. If you will look at the curves that have been made, you will see that as man reaches the point of his greatest mental activity, the brain tumors and things of that kind become relatively rare. Why is that? Why is it, also, that in the digestive system there are far more tumors than one would expect in risks of that system? That system has been developed for a diversified diet. We have had a long evolution to teach our stomach how it can be maltreated biologically and chemically, and yet it has far more than its share of the malignant tumors that occur in the life history of human beings. Is there, therefore, any relationship between the discharge of nervous activity and the excess of tumors of the digestive tract? I should say that a careful study of people of different levels of nervous ability, mental ability, and mental and nervous activity, would be very desirable, also a study of cancer of the stomach in feeble-minded people who are cases of arrested development, intensive studies of cancer of the stomach in different types of insanity, in epileptics, in large populations of these types of people gathered from all over the country by those interested. We can make an experimental population, by the accumulation of scattered data so that these things could be lumped and studied. I think perhaps that sort of thing might be helpful.

Dr. Alvarez: I should like to say a word in favor of the study of coroners' material. All my life I have regretted the wastage of the most valuable necropsy material that we probably have in this world for the study of medicine, and this is the material in big morgues where men are being brought in every hour, stabbed in the back, fallen off a telegraph pole, or run over by an automobile. The most fascinating lesions are to be found in such persons, and we can learn so much from such discoveries about the beginnings of disease.

In many a coroner's office the work is done crudely and perfunctorily, perhaps by a political appointee who gets $200 a month. All he tries to do is to establish the cause of death. Possibly if some money were to be spent, we could change some of these big morgues into wonderfully helpful institutions.

I have often thought that we ought to have men roaming around the world studying the incidence of cancer among peoples who have peculiar diets. For instance, in India one can find two peoples living side by side—one, vegetarian in habits, and the other, meat eaters. Of course, anyone hoping to carry out a useful study of this type should have a good training in logic and statistics.

To show what I mean: An able physician who is head of the biggest hospital in Korea noticed that he practically never saw cases of gall-bladder disease. Then it occurred to him that he wasn't seeing older women. They were afraid to consult the "foreign devil." He realized that he could not compare his figures with those of a hospital in this country unless he could correct for the age incidence, particularly of the women patients.

It seems to me that it is to a large extent a waste of time to work for months gathering figures if, when we get them, we can't be sure what they mean. I think we must always have along side of us some hard-boiled, well-trained statistician who will constantly be saying, "Have you controlled this factor or that factor?" Many a time at the Mayo Clinic I have started a statistical study but have not finished it because when we came to hunt for a control group we didn't know how to get one that was trustworthy.

There is another difficulty with many of these statistical studies based on material gathered by persons who did not intend to analyze the data. Usually, if the study is to be of value, the data should be collected by a trained statistician who knows what he is going to do later. For instance, one of my friends at the Mayo Clinic once started a statistical study to see if gallstone disease was correlated closely with duodenal or gastric ulcer. All he did was to send a girl down to the statistical room to go over 200 cases and see what the correlation was. She returned with some very nice clear-cut results. He was about to publish this study when I heard about it. Not knowing about his work, I had been down in the record room night after night trying to get an answer to this question myself. I soon decided that the only way in which to get accurate data was to study the records made by the surgeons, but almost immediately I became stalled because in a high percentage of cases the surgeon was so busy removing an ulcer that he didn't comment about the condition of the gall bladder. In other cases the gall bladder had already been removed, and I couldn't tell whether its removal had been justified or not. Worse yet, when the surgeon did comment on the condition of the gall bladder, I found some 15 different types of statement. Some of these left no doubt as to the condition of the gall bladder, but in many cases it was obvious that the surgeon was not sure if the organ was diseased, or if so, how diseased it was. As a result I had to give up. I couldn't get any answer to the question that satisfied me. But as I said before, a technician promptly got a clear-cut answer. The difficulties didn't worry her. The principal point I want to make is that for satisfactory research the surgeon should have been interested in answering the question. Then the data would have been at least complete.

Dr. Voegtlin: In connection with the dietary aspect which Dr. Alvarez has raised, you probably are familiar with the work of Bonne in the Dutch East Indies on Malays and Chinese. I believe it is the best kind of attempt that has ever been made to correlate gastric cancer with race and diet. Malays show a low mortality from cancer of the stomach, and the Chinese have a high one. He found a very striking difference in the diets of the two

races. The diet of the Malays is largely vegetarian, the Chinese eat much pork and animal fats and proteins. There is also a racial factor. The two races do not intermarry, so you really have there a genetic difference. What part the genetic factor plays remains to be determined. I therefore agree with Dr. Alvarez that in order to study these questions, investigations must be done in places where conditions are suitable, and even then it will be difficult to get a sound answer.

Chairman Murphy: Dr. Voegtlin has suggested three headings under clinical studies. Would anybody like to comment under section 3, if there is no more discussion on the first section?

Dr. Brunschwig: I should like to make one suggestion in regard to the study of gastric secretion following partial gastrectomy for carcinoma. Gastric analyses after the Billroth II or Polya operation are not satisfactory because of the regurgitation of intestinal contents into the stomach. If, after partial gastric resection, a Y-type of gastroenterostomy or Roux operation is done, regurgitation will be minimal and the gastric contents recoverable will represent to a great extent the secretion of the remaining gastric mucosa. In this way more accurate information can be obtained as to whether or not gastric acidity will return once achlorhydria is established with gastric cancer. My feeling is that the stomach will remain achlorhydric, but we do not have as yet good evidence on this question.

Chairman Murphy: Perhaps a better plan would be to ask the members of the conference if they would be willing to formulate, each from his point of view, methods and organization for an attack on this important problem. Such plans as might be evolved could be sent to the Council for consideration and study. Perhaps this body could aid in a proper project or interest the foundations and individuals in developing a constructive program.

In my opinion, suggestions should be on broad lines for it is probable that progress will best be made by proper coordination between groups of workers. It is unlikely that any one clinic could gather sufficient material in 2 or 3 years to be of statistical value; yet if several groups were cooperating with uniform methods, significant information for investigation might eventuate in a much shorter period.

Would the members of the conference consider sending in to the Council their individual ideas as to how a program for the study of gastric cancer should be developed?

Is there any discussion of this suggestion, and would the members of the conference be willing to undertake such step?

Dr. Alvarez: Send them when we get back to our desks?

Chairman Murphy: Yes.

Dr. Alvarez: If you remind us.

Chairman Murphy: I think we might undertake to remind you—but it seems to me such an important phase of the whole cancer problem—that every step should be made to foster investigation, to crystallize the particular points to be investigated, and to attempt to support any suggested organization to solve the immediate problems.

I think it might be interesting to hear from some of the foundation people. Dr. Bayne-Jones.

Dr. Bayne-Jones: I have very little to say, except, in the first place, to express gratitude to the organization for allowing me to attend, and to say that from my point of view I have been intensely interested in seeing what we could do to study cancer in human beings, where the problem lies really, where the main interests are, where the conditions are peculiar to that kind of animal, and I think this is a very hopeful

and important move in advance toward the whole observation of cancer of the stomach in the human being. We shall certainly get somewhere from a conference like this, and the pooling of our interests and information.

The plan Dr. Murphy suggests and the one Dr. Voegtlin suggests appeal to me, that material be gotten together and suggestions sorted out, and perhaps those suggestions will include the establishment of a gastric cancer registry, a mechanism for passing around this information, and will bring together the groups working in this field. The foundation that I represent is already interested financially and otherwise in the study of various dietary and nutritional factors and hormonal factors that operate in the human being, and one part of that is cancer of the stomach.

Chairman Murphy: Before we adjourn, I should like to express the appreciation of the Council for the attendance at this conference and for the great deal of thought and work that has been put into the preparing of the material which you have presented. I consider that it was well worth while from our point of view, and that very important developments in the study of cancer will eventuate.

With no further comment, we shall consider the meeting adjourned.

(The meeting adjourned at 3:25 p. m.).

Experimental Gastric Carcinoma: A Critical Review with Comments on the Criteria of Induced Malignancy[a b c]

By Alfred J. Klein, *M. D.*, and Walter Lincoln Palmer, *M. D.*

INTRODUCTION

The production of experimental cancers is now generally considered to have started in 1914 with the finding of Yamagiwa and Ichikawa that repeated applications of coal tar to a rabbit's ear was followed in some cases by carcinomatous changes with metastasis. Since that time many different neoplasms have been produced experimentally by various methods. The studies of Kennaway, Cook, their co-workers and others in the isolation of a carcinogenic hydrocarbon from tar and later in the preparation and synthesis of other carcinogenic compounds opened up new methods of approach. In view of the rapid strides made in the past twenty-five years in the field of experimental cancer, it seems of interest to review what success has attended efforts to produce experimentally one of the most common malignant growths found in man—carcinoma of the stomach.[1]

In animals, carcinoma of the stomach is one of the rarest spontaneous cancers. Feldman [2] estimates that 8 to 10 per cent of old dogs have neoplasms, of which 40 to 50 per cent are malignant; yet all studies of the occurrence of spontaneous cancers in domestic, laboratory and wild animals uniformly show that carcinoma of the stomach is rare (Wells, Slye and Holmes [3]; Slye, Holmes and Wells [4]). There is no strain of animal in which gastric cancer develops regularly or indeed with sufficient frequency to warrant an attempt to develop a "cancer strain". Furthermore, the diagnosis for animals is almost invariably made post mortem.

In over 142,000 mice of the Slye stock, dying of natural causes, Wells, Slye and Holmes [3] reported 12 gastric cancers: 8 squamous cell carcinomas, 3 adenocarcinomas and 1 sarcoma. In addition there were 2 adenomas which may have been early adenocarcinomas. This represents all the gastric cancers in the Slye stock of mice in over twenty years of careful observation. This report, essentially confirmed by all other investigators, stresses the rarity of spontaneous gastric neoplasms in mice.

Stewart and Andervont [5a] found that in mice of both sexes of strain I there regularly develop spontaneous adenomatous, hypertrophic and hyperplastic overgrowths of the glandular rugae of the pyloric portion of the stomach with associated inflammatory changes and ulceration; metastases have not been observed. Histologic

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[a] *"Reprinted, with additions, from the Archives of Pathology, June 1940, Vol. 29, pp. 814–844. Copyright, 1940, by American Medical Association." Reproduced, without changes, through the courtesy of Archives of Pathology and of the American Medical Association.*

It is felt that the reprinting of this paper will assist the reader of these proceedings to obtain a comprehensive view of the experimental phase of the problem.

[b] *From the Department of Medicine, University of Chicago.*

[c] *This review is preliminary to work aided by a grant from the Fenger Memorial Fund.*

[1] *References to some work, particularly that pertaining to parasitic tumors, are chiefly to key articles. If the same paper has been published in several languages or journals, only one reference is usually made to it.*

[2] *Feldman, W. H.: Neoplasms of Domesticated Animals, Philadelphia, W. B. Saunders Company, 1932, p. 68.*

[3] *Wells, G. H.; Slye, M., and Holmes, H. F.: Am. J. Cancer 33: 223, 1938.*

[4] *Slye, M.; Holmes, H. F., and Wells, H. G.: J. Cancer Research 2: 401, 1917.*

[5] *(a) Stewart, H. L., and Andervont, H. B.: Arch. Path. 26: 1009, 1938. (b) Stewart, H. L.: ibid. 29: 153, 1940.*

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studies revealed some features somewhat suggestive of malignant growth. A few adnomatous tumors in the lungs were regarded as nonmetastatic, since in mice of this strain such pulmonary tumors develop spontaneously. Many etiologic factors were given serious consideration by these investigators, but no positive conclusion was reached. The condition, it is pointed out, bears some analogy to a rare gastric adenopapillomatosis occurring in man and apparently having a familial tendency.

In marked contrast to the rarity of gastric cancer in animals is the well known frequency of carcinoma of the stomach in man. Livingston and Pack [6] estimated that 40,000 to 50,000 deaths are caused annually in the United States by gastric carcinoma. This is from 25 to 30 per cent of deaths due to malignant tumors, or about 3 per cent of all deaths. The mortality statistics of some European countries show that more than one half of all malignant neoplasms are carcinoma of the stomach (Konjetzny [7]).

In attempting to explain the marked difference between man and the lower animals in the development of spontaneous gastric cancer, attention naturally centered on the diet and on the fact that man is the only animal to heat his food and to consume it hot. In 1916 Lerche [8] analyzed the situation somewhat as follows: He reviewed statistics of the sites of carcinoma in the esophagus and stomach and the sites of cicatricial strictures resulting from swallowing corrosive fluids. The predisposition of certain sites to stricture formation following the ingestion of corrosive fluids was found to depend on the time of contact of the fluid with the various portions of the esophagus and stomach. Evidence was presented to show why cicatricial strictures do not occur at the sites of the physiologic narrowings but above them and why in cases in which a small amount of corrosive fluid was taken the esophagus escaped stricture formation entirely and only the antral area of the stomach was involved. The latter involvement was more frequent in nonfatal cases. It is significant that the favorite sites of carcinoma of the esophagus and stomach were found to correspond exactly to the favorite sites of cicatricial strictures in these organs. Since the explanation of the localization of corrosive action to certain areas depended on the mechanics involved when a fluid is ingested, it seemed reasonable to suspect some fluid used by man and not by animals as an etiologic factor in the production of carcinoma of the esophagus and stomach. Alcohol and other fluids were considered, but hot liquids remained as the most likely possibility.

Bonne [9c] had the unique opportunity to study two groups living in the same country with a marked difference in the incidence of gastric carcinoma: the Malays in Java, in whom gastric carcinoma is almost unknown, and the immigrated Chinese in Java, in whom it is not uncommon. In 3,885 autopsies on these Malays over a period of fifteen years, about three fourths of whom were males, only 1 gastric carcinoma was found, although the total cancer rate when recalculated for a population of standard age was found to be in accord with the usual figures for Western countries. Bonne and co-workers [9d] found

[6] *Livingston, E. M., and Pack, G. T.: End Results in the Treatment of Gastric Carcinoma, New York, Paul B. Hoeber, Inc., 1939.*

[7] *Konjetzny, G. E.: Der Magenkrebs, Stuttgart, Ferdinand Enke, 1938.*

[8] *Lerche, W.: Surg., Gynec. & Obst. 23: 42, 1916.*

[9] *(a) Bonne, C.: J. Trop. Med. 29: 288, 1926; (b) Ztschr. f. Krebsforsch. 25: 1, 1927; (c) Am. J. Cancer 30: 435, 1937. (d) Bonne, C.; Hartz, H.; Klerks, J.V.; Posthuma, J. H.; Radsma, W., and Tjokronegoro, S.: ibid. 33: 265, 1938. (e) Bonne, C., and Sandground, J. H.: ibid. 37: 173, 1939.*

no significant difference in the morphologic character of the stomach or in the gastric secretion in these two groups. They carefully studied the dietary and other habits but were unable to draw definite conclusions. Somewhat similar studies have been reported repeatedly, for example, those of Herbert and Bruske [10] and Lintott,[11] who, in attempting to account for the fact that the incidence of gastric carcinoma in Holland was twice that in England, concluded that an extrinsic factor was involved.

EXPERIMENTAL GASTRIC CARCINOMA

The animals almost universally used in reported investigations of experimental gastric carcinoma are mice and rats. Both the mouse and the rat have a stomach consisting of two chambers: (1) a forestomach comprising two thirds of the entire stomach and lined by squamous epithelium continuous with the esophagus and (2) a glandular stomach separated from the upper squamous-lined portion by a slight elevation, the limiting ridge.

Obviously two entirely different types of carcinoma might develop: (1) a squamous cell carcinoma of the nonsecreting forestomach, which would appear to be more closely related to a carcinoma of the esophagus or skin than to (2) an adenocarcinoma of the secreting glandular stomach. A sharp distinction between these two unrelated types should be made.

The means used in attempts to produce experimental gastric carcinoma generally fall into one of the following categories: (1) dietetic irritants, (2) parasites, (3) dietary deficiencies, and (4) agents known or suspected to be carcinogenic when fed, injected or implanted.

[10] *Herbert, W. E., and Bruske, J. S.: Guy's Hosp. Rep. 86: 301, 1936.*

[11] *Lintott, G. A. M.: Guy's Hosp. Rep. 86: 293, 1936.*

Dietetic Irritants.—The only attempt to produce gastric cancer experimentally by hot food was made by Lewis[12] a good many years ago. He poured hot mush daily into the gastrostomies of 35 dogs. Unfortunately, none of the dogs survived this procedure more than one year. No evidence of gastric carcinoma, gastric ulcer or gastritis was found. If this procedure could lead to changes eventually resulting in gastric carcinoma, it is now known, as pointed out by Wells, Slye and Holmes,[3] that it would probably require a longer time than these dogs survived. Experimental cancers of any kind are rare in dogs, but Passey's[13a] recent observation of a malignant melanoma occurring in a dog after six and one-half years of weekly tarring may give some indication of the induction period required.

Parasites.—The earliest attempts at experimental production of cancer to attract wide attention were those of Fibiger, who in 1913 published the first of a series of beautifully illustrated reports on the production of squamous cell carcinoma in the forestomachs of rats by means of a nematode, Gongylonema neoplasticum.[14] Much of this work has been criticized and remains unconfirmed (Passey, Leese and Knox[13b,c]; Cramer[15]).

Fibiger found squamous cell tumors in the forestomachs of wild rats infected with Gongylonema neoplasticum (Spiroptera neoplastica). Rats contracted the infection from cockroaches. Fibiger fed infected cockroaches to black and white laboratory rats and maintained them on a diet of white bread and water. After infection none of the rats lived more than

[12] *Lewis, J. H., cited by Wells, Slye and Holmes.*[3]

[13] *(a) Passey, R. D.: J. Path. & Bact. 47: 349, 1938. (b) Passey, R. D.; Leese, A., and Knox, J. C.: ibid. 40: 198, 1935; (c) 42: 425, 1936.*

[14] *Fibiger, J.: Ztschr. f. Krebsforsch. (a) 13: 217, 1913; (b) 14: 295, 1914; (c) J. Cancer Research 4: 367, 1919.*

[15] *Cramer, W.: Am. J. Cancer 31: 537, 1937.*

two hundred and ninety-eight days. The changes in the stomach were limited to the squamous-lined forestomach. The glandular portion was never involved either primarily or by invasion. The stomach was often enlarged, with nodular prominences on the external surface. The gastric mucosa had obvious papillary growths, and metastases were reported in the lungs of some rats. Microscopically, simple hyperplasia, hyperkeratosis and slight papillary downgrowths of the squamous epithelium were found in almost all rats. These changes were regarded as benign. In addition, over 50 per cent of the rats had changes interpreted as carcinomatous. In the first 111 rats reported on, Fibiger found, according to his criteria, 19 cases of squamous cell carcinoma, and later he observed similar cases in other rats. The changes in the forestomach were classified as malignant when the following conditions were present: (1) downgrowth of atypical and keratinized epithelial cells in abundance, arranged as spherical masses and horny globes; (2) infiltrative growths of these into the deeper layers, splitting up invasively the connective tissue of the mucosa and the muscle cells of the muscularis mucosae and also penetrating into the superficial and deeper layers of the submucosa. Neither infiltration of the muscularis or neighboring structures nor metastases were required for the designation of the tumors as malignant. As a matter of fact, the muscularis was not invaded even in those cases in which metastases were reported. Whether these represented actual metastases to the abdominal lymph nodes and the lungs is open to serious doubt. Lymph nodes similar to those believed by Fibiger to have metastatic deposits have been observed in the absence of malignant growth. Lesions in the lungs similar to those regarded as metastases have been seen repeatedly in rats without gastric lesions. They are usually bronchiectatic cavities or metaplastic epithelium.[13e]

As Cramer[15] recently pointed out in an excellent review of the subject, Fibiger's results have rarely been questioned, although many investigators seriously doubt his interpretation of the lesions as malignant. In the final analysis, much depends on whether metastases took place. Fibiger pointed out that the metastases to the lymph nodes were only microscopic, but the microscopic appearance of the so-called metastases is not conclusive.

Fibiger[14e] later reported a squamous cell carcinoma in the forestomach of a mouse 20 to 22 months old which died four hundred and twenty-eight days after Spiroptera infection. The tumor involved all layers of the stomach and invaded the liver, spleen and diaphragm. Numerous metastases were found in the abdomen. The metastases were successfully transplanted through four generations covering a period of one year, in the cases of 28 of the 55 mice that survived inoculation, and maintained the histologic features of the original gastric tumor. Fibiger regarded this as the same type of lesion he had observed in rats and emphasized the fact that this mouse lived more than four months longer, after Spiroptera infection, than any rat and that therefore the advanced characteristics of a malignant tumor had time to develop. Passey, Leese and Knox,[13b] however, succeeded in keeping rats on a complete diet alive for four hundred and eighty days after infection with Gongylonema neoplasticum and observed only slight mucosal changes in the forestomach. This suggests that the Spiroptera infection in itself is not sufficient to cause the gastric lesions. There is little doubt that the gastric tumor in the mouse reported by Fibiger was a squamous cell carcinoma, for the muscularis and neighboring organs

were invaded, and transplantation of the metastases was successful. Fibiger never reported a similar tumor in a rat, although a few similar but not as well established ones were found in mice.

Passey, Leese, and Knox [13b] recently repeated Fibiger's experiments. As already mentioned, in a group of rats on a complete diet infected with Gongylonema neoplasticum the mucosal changes in the forestomach were insignificant. In a group of rats fed Fibiger's diet of white bread and water some lesions occurred in the forestomach, although they were not as severe as those seen in a similar group infected with Gongylonema neoplasticum. No gastric carcinoma, however, was found in any rat. Similar results were obtained in rats on a diet deficient in vitamin A with added parasitic infection. These investigators pointed out that Brumpt had observed only 1 gastric carcinoma in 781 wild rats found infected with Gongylonema neoplasticum and had failed to obtain a single carcinoma in 31 laboratory rats and 5 white mice experimentally infected with the parasite.

Bullock and Rohdenburg [16] believed that the lesions of the forestomach observed by Fibiger were benign and the result of nonspecific chronic irritation. They devised many ingenious experiments to test this hypothesis. They were unable to duplicate Fibiger's results exactly but produced a close resemblance. Three types of gastric irritation were used: (1) mechanical, (2) chemical and (3) a combination of the two.

A celluloid ball covered with pig's bristles was introduced into the rat's forestomach through a gastrotomy and suspended by a string. Within a few weeks irregular polypoid growths were observed, most marked at the site of incision. In control experiments, however, in which a simple purse string suture was taken in the stomach wall, without making an incision, the same changes were sometimes noted. In addition such polypoid growths were seen in some rats that were not operated on. When a cork ball with protruding pinpoints, covered with celluloid and keratin, was introduced into the stomach through a gastrotomy and allowed to remain free in the gastric cavity, lesions were usually found in the glandular chamber of the stomach and were more severe when the gastrotomy had been in the glandular portion. The changes consisted of an increase in the mucous cells and a complete absence or scarcity of the parietal cells with downgrowths of glandular epithelium forming cystadenomas and accompanied by varying degrees of inflammation of the gastric wall. It is interesting that in some cases osteoid tissue was found in the connective tissue of the stratum proprium. When a rubber sponge impregnated with scarlet red powder or pine tar was introduced into the stomach, hypertrophy and proliferation of the squamous epithelium, especially around the gastrotomy, took place and sometimes penetrated the muscularis mucosae. Similar changes were found after scarlet red or pine tar in oil or ether had been injected directly into the stomach wall. Although the factor of a food deficiency may have played some role in these results, Bullock and Rohdenburg clearly showed that lesions of the forestomach resembling those observed by Fibiger could be produced in the absence of parasites. Furthermore, the well illustrated benign cystadenomatous lesions in the glandular stomach form an instructive basis of comparison with similar lesions which have at times been reported as malignant.

Yokogawa [17] reported the experimental

[16] *Bullock, F. D., and Rohdenburg, G. L.: J. Cancer Research 3: 227, 1918.*

[17] *Yokogawa, S.: Gann 18: 48, 1925.*

production of squamous cell carcinoma in the forestomach of the rat by means of another nematode, Gongylonema orientale. Carcinoma was reported to have developed in 3 of 61 white rats after at least two hundred days of infection. The characteristics of these tumors were in all essential respects similar to those observed by Fibiger. The tumors were papillomatous growths which at their base extended down through the muscularis mucosae into the submucosa but did not involve the muscularis. Invasion of lymphatic spaces was present. The glandular portion of the stomach showed some atrophic change but was otherwise not involved. Metastases to the liver and lung were reported in one of the rats. Yokogawa described these metastases grossly as hard grayish spots containing a cheesy material. Microscopically, the cavities were lined in part by laminated flat cells. Yokogawa recognized that such lesions were sometimes found in rats without cancer but thought the evidence in this particular case pointed to metastases. A photomicrograph of one such lesion leaves some doubt whether this was actually a metastasis. Yokogawa's observations are essentially similar to those of Fibiger, and their interpretation is open to the same objections.

Bonne[9a] reported a squamous cell tumor in the forestomach of a wild rat caught in Italy and found infected with a nematode, Hepaticola gastrica. The tumor was a papilloma the size of a cherry. Microscopically, the muscularis mucosae was penetrated by an epithelial downgrowth, but the muscularis was uninvolved. The glandular stomach was normal. No metastasis was found. Evidence that this was a malignant growth rests chiefly on the fact that the tumor invaded some blood vessels. Bonne pointed out the close resemblance to Fibiger's tumors and the probability that the nematode infection of the stomach was casual rather than coincidental. Whether this represented a true cancer of the forestomach can be questioned.

Vogel [18] later experimentally inoculated rats with Hepaticola gastrica. Although he failed to obtain infection of old rats, he succeeded in producing infections in 4 young ones, in 2 of which squamous cell carcinoma of the forestomach was reported to have developed after three months. Vogel noted that there was considerable similarity to the lesions observed by Fibiger with the exception of a greater tendency toward epithelial downgrowth into the submucosa and a lesser amount of papillomatosis into the lumen. The muscularis was not involved, and the glandular stomach was normal. Metastases are not mentioned. Vogel stressed the fact that no parasites were found in the tumors when the animals died and regarded this as evidence that a true malignant growth was present in that after the malignant change had taken place it persisted without the presence of the causal agent. Although this is one explanation it is not by any means the only one.

Bonne and Sandground[9e] recently noted the association of a "gastric adenoma bordering on malignancy" and a nematode, Nochtia nochti, in Javanese monkeys. The adenoma was never observed in the absence of the parasite, and whenever the parasite was found, an adenoma was present. These authors succeeded in inoculating monkeys with Nochtia nochti and producing such tumors experimentally. No metastases were observed, but definite invasion of blood vessels was noted. Whether these adenomas can develop into adenocarcinomas remains an open question.

Comment: A review of gastric parasitic infections does not disclose conclusive evidence that infection in itself leads to gastric tumors in spontaneously or experimentally

[18] *Vogel, H.: Ztschr. f. Krebsforsch. 29: 351, 1929.*

infected rats. The tumors observed in such animals may be due primarily to other factors not satisfactorily eliminated in the experiments, such as dietary deficiencies. When Passey, Leese and Knox[13b] inoculated rats maintained on a complete diet with Spiroptera neoplastica, insignificant gastric mucosal changes resulted. It is therefore not surprising that some investigators found more severe gastric lesions in young and growing rats than in old ones. In the interpretation of reports, due allowance should be made for the variation of different species and strains of animals in their reaction to the same dietary deficiency or parasite. The role of nematode infections in the genesis of forestomach lesions in rats seems to be that of aggravating mucosal changes initiated by other causes, although parasites, as is well known, can cause tissue proliferation and malignant growth in other organs. Hoepple,[19] in a comprehensive review of parasites and tumor growth, discussed the various mechanisms by which this may occur. Bonne and Sandground's[9e] observations indicate, however, that in monkeys inoculated with Nochtia nochti gastric adenomas occur only in the presence of parasitic infection.

Regardless of the exact cause of the gastric squamous cell tumors attributed to parasites, it is of interest to consider the evidence of the malignant nature of these lesions. Fibiger's[14c] clearly stated criteria of malignancy, previously mentioned, will be more fully considered later. It is, however, generally accepted at present that his criteria are inadequate. Whether such changes can be regarded as "precancerous" will remain an open question until it is possible to observe more frequent transition to undoubted malignancy. Fibiger reported squamous cell tumors in a few mice, one of which was supported by practically conclusive evidence of malignancy; however, in view of the large number of animals used in Fibiger's work the possibility of spontaneous malignancy was not entirely eliminated. The causal relation between gastric squamous cell carcinoma, parasites, and other factors that may have been unknowingly involved needs to be demonstrated more regularly to be convincing.

Dietary Deficiencies.—Dietary deficiencies may seem unrelated to experimental gastric carcinoma, but the severe changes in the forestomach apparently caused by such deficiencies, particularly in rats, have been reported at times as malignant. Furthermore, because these severe changes closely simulate those sometimes interpreted as carcinoma and attributed to other causes, a food deficiency should be considered as a possible factor in some of the reports of experimental gastric carcinoma.

Pappenheimer and Larimore,[20a] in 1923, were the first to call attention to the possible relation of forestomach lesions in rats to a dietary deficiency. Their preliminary evidence suggested that vitamin A deficiency might be the cause. Further study,[20b] however, revealed that the lesions were present when sufficient ultraviolet radiation was given to prevent rickets. The lesions were uncommon in rats on a complete diet, and when present, were mild. When rats were placed on a diet known to bring about the forestomach lesions, neither the addition of cod liver oil nor of Osborne and Wakeman's yeast extract nor changes in the mineral content of the diet prevented them. Pappenheimer and Larimore concluded that a food deficiency was a factor in the appear-

[19] *Hoepple, Chinese M. J. 47: 1075, 1933.*

[20] *Pappenheimer, A. M., and Larimore, L. D.: (a) Proc. Soc. Exper. Biol. & Med. 21: 141, 1923–1924, (b) J. Exper. Med. 40: 719, 1924.*

ance of the gastric lesions but were unable to determine what element of diet was lacking. They observed that rats on a deficient diet often had hair in their stomachs and suggested that this hair might aggravate the lesions. Of 6 rats fed a complete diet mixed with ground-up hair, 2 were found to have benign changes of the forestomach and ulcers, with hair embedded in the stomach in such positions as to indicate that it was a factor in the production of the ulcers. The lesions observed by Pappenheimer and Larimore were limited to the forestomach, usually to an area near the elevated ridge separating the forestomach from the glandular stomach, and consisted essentially of papillomatosis. The changes were considered benign.

Wolbach and Howe [21] in 1925 reported change caused by vitamin A deficiency in rats. They took precautions to prevent any deficiency other than vitamin A by forced feeding whenever necessary, particularly after anorexia and impairment of the sense of smell developed. No significant gastric lesion was observed in spite of extensive changes in other covering epitheliums. Wolbach and Howe found large bronchiectatic cavities in many of the rats, which were often considered the immediate cause of death. Although tissue changes in the stomach were not found, the alteration in the covering epithelium caused by vitamin A deficiency is worth noting: "Growth activity of the epithelium is not diminished; on the contrary, there is convincing evidence that it is greatly augmented. In a few of our animals, the behavior of the replacing epithelium in respect to numbers of mitotic figures and response on the part of connective tissue and blood vessels suggests the acquisition of neoplastic properties." Because of the thoroughness of this work, the observations in relation to the stomach and lungs seem particularly significant. It has been suggested that the so-called metastases to the lungs in rats with gastric tumors were sometimes bronchiectatic cavities. That such cavities do appear in rats without any pathologic changes in the stomach was clearly shown by Wolbach and Howe and has been repeatedly confirmed by others.

Fujimaki [22a, b] in 1926 observed severe papillomatosis of the forestomach in young rats on a vitamin A-deficient diet. The lesions were believed to be malignant. One of 5 rats with the most severe gastric papillomatosis was reported to have metastatic nodules in the lung. One of these metastases is illustrated.[22b] The gastric lesions consisted essentially of hyperkeratosis and downgrowth of atypical epithelium with penetration of the muscularis mucosae. The muscularis was not invaded. The glandular stomach was normal. An accompanying editorial note states that microscopic examination of Fujimaki's slides, from which the photomicrographs were prepared, left some doubt as to the malignant nature of the changes.[22a] In a more recent publication Fujimaki and co-workers[22c] offered evidence to show that various fatty acids and lipoids in the diet are factors in the appearance of atypical epithelial proliferation of the forestomach in rats and that vitamin A (butter) does not prevent it.

Cramer's [15] experiments with vitamin A-deficient rats are worthy of note for two reasons. First, the severe papillomatosis of the forestomach was considered benign, and, second, two experiments done ten years apart, with apparently identical methods except that different strains of rats

[21] *Wolbach, S. B., and Howe, P. R.: J. Exper. Med. 42: 753, 1925.*

[22] *(a) Fujimaki, Y.: J. Cancer Research 10: 469, 1926; (b) Gann 21: 8, 1927. (c) Fujimaki, Y.; Arimoto, K.; Kimura, T.; Ohba, K., and Matsuda, G.; Tr. Jap. Path. Soc. 21: 708, 1931.*

were used, showed a startling difference in results. Cramer stated that if the earlier sections of the stomach had not been available for reexamination he himself could hardly have believed that the benign papillomatosis, as marked as that observed by Fibiger, could have been so severe in the first experiment and so mild in the second. He has no explanation to offer except that different strains of rats react in varying degrees to vitamin A deficiency or that the papillomatosis of the forestomach may be due to a virus the action of which is enhanced in rats on a deficient diet.

Hoelzel and Da Costa [23] offered a hypothesis of the genesis of the forestomach lesions in rats observed by them without postulating any specific food deficiency. They found that rats on a low protein diet when fed alternately for two days and starved for two days had ulcers of the forestomach after two weeks. These authors stressed the presence of the ulcers, although some papillomatosis apparently also was present. The simplest method of producing such lesions was found to be starvation. Inanition alone, however, did not cause the ulcers to persist, as shown by the fact that they healed readily on a bran diet which had no caloric value. Ulcers also developed in rats on a bread diet. The incidence of the ulcers decreased when 15 to 30 percent calcium carbonate was added to the bread. Ingestion of hair seemed to cause ulceration only when this interfered with a normal intake of food. Their observations led them to conclude that the acid-combining properties of the food largely determined the amount of ulceration and that the acid gastric juice probably acted as an irritant in the manner shown by Bullock and Rohdenburg [16] by artificial irritation.

Rats fed a high fat, low protein diet by Hoelzel and Da Costa [23b] were found to have a particularly prominent overgrowth of the mucosa of the forestomach. This observation is similar to that of Fujimaki and co-workers,[22c] who found that an increase in papillomatosis resulted in rats fed various fatty acids and lipoids. Because these lesions resembled those previously reported by some investigators as malignant, Hoelzel and Da Costa made a study of the morphologic changes and found that grossly they consisted of nodular prominences on the outer surface of the stomach with ulceration and overgrowth of the mucosa. Microscopically, the largest nodules were found to be epithelial cysts, generally located at the limiting ridge. Other nodules consisted of cornified globular masses. In most cases continuity with the normal epithelial layer could be demonstrated. Although there was a downward growth of the epithelium, the muscularis was never invaded. Observations on 7 rats which were fed alternately in a manner that produced ulcers and nodules in control rats and which then were given a complete diet indicated that these rather severe changes were reversible. The ulcers disappeared faster than the nodules or epithelial cysts, but even these seemed to disappear eventually. Hoelzel and Da Costa concluded that the lesions were not malignant. It is unknown whether they would have become malignant in a more prolonged experiment.

Harde [24] reported a squamous cell carcinoma in the forestomach of a mouse fed a deficient diet for seven months. Because of a paratyphoid infection at the end of this time, a complete diet was given and continued until the mouse died seven months later. A squamous cell

[23] *Hoelzel, F., and Da Costa, E.: Proc. Soc. Exper. Biol. & Med. (a) 29: 382, 1931; (b) 29: 385, 1932.*

[24] *Harde, E.: Compt. rend. Soc. de biol. 110: 245, 1932.*

tumor, 1 by 2 cm., was found in the forestomach, which infiltrated all layers of the gastric wall and invaded the liver. In addition there was adenomatosis of the glandular stomach, which infiltrated the submucosa. Whether metastases were present is not known. There is no illustration. Harde made no attempt to correlate the experimental procedure with the appearance of the carcinoma since this was the only cancer in over 600 mice.

Findlay[25] in 1928 reported lesions in rats due to vitamin B_1 and vitamin B_2 deficiency. He found papillomatosis, consisting of thick layers of squamous cells with exfoliation of the keratin layer, in the forestomach of every rat fed a diet deficient in vitamin B_2. The epithelium formed papillary projections into the lumen, and blunter processes extended downward as far as the muscularis mucosae. There were numerous mitotic figures. Ulceration of the superficial layers of the mucosa was present. No evidence of malignancy was found. Such gastric changes were never present in rats on vitamin B_1 deficiency only. Findlay agreed with Pappenheimer and Larimore that the ingestion of hair might afford a plausible explanation of the lesions, since vitamin B_2-deficient rats shed large amounts, which inevitably contaminated the diet. Among other lesions found in vitamin B_2-deficient rats, Findlay reported profound changes in the squamous epithelium of the skin, consisting of active mitosis in the cells of the stratum granulosum, while the whole process of keratinization was excessively active. All the changes are well illustrated.

Sharpless[26a] observed lesions developing in the forestomachs of rats within three months after they were placed on a low casein diet. These lesions were described essentially as thickening of the epithelial ridges with papillomatosis, hyperkeratosis and ulceration of the mucosa, most marked along the limiting ridge. No metastases were observed.

In a later report Sharpless[26b] described hyperplastic changes of the forestomach in all of the 125 rats fed a low casein diet and no such lesion in 200 control rats on a complete diet. This stock of rats has shown no spontaneous malignant tumor in over four years. Control rats fed the same diet with the addition of 12 per cent vitamin-free casein or 0.2 per cent cystine showed no lesions. When given a low casein diet with the addition of 10 per cent gelatin, to approximate the physical properties of a diet without a protein deficiency, the lesions appeared as though a low casein diet only had been fed. The papillomatosis in some instances almost occluded the lumen. In cases of long standing, spurs of atypical keratinizing epithelium sometimes penetrated the muscularis mucosae, extending into the submucosa, and proliferated, forming cysts. Active invasion of the muscularis was reported in some rats. As many as eighteen mitotic figures were observed in one high power field. No metastases were found. One of several photomicrographs has a legend suggesting a malignant process. Sharpless regarded some of these lesions as malignant; however, the evidence has been considered inadequate.[26c]

Howes and Vivier [27] reviewed the relation of diet to the occurrence of gastric lesions in rats and the interpretation of these changes. In their own work they found that whole yeast prevented the forestomach lesions when added to the diet used by Pappenheimer and Larimore to produce them, whereas the addition of Osborne and Wakeman's yeast extract, vitamin-free

[25] *Findlay, G. M.: J. Path. & Bact. 31: 353, 1928.*

[26] *Sharples, G. R.: (a) Proc. Soc. Exper. Biol. & Med. 34: 684, 1936; (b) Ann. Surg. 106: 562, 1937; (c) abstracted, Am. J. Cancer 37: 457, 1939.*

[27] *Howes, E. L., and Vivier, P. J.: Am. J. Path. 12: 689, 1936.*

casein, cod liver oil or other forms of vitamin A was of no protective value. The gastric changes observed when whole yeast was not added to the diet were essentially hyperplasia, hyperkeratinization and ulceration of the squamous epithelium in the forestomach, with hypertrophy of the limiting ridge. Similar lesions without keratinization were found in the glandular stomach. Mitotic figures were numerous. The muscularis mucosae was thinned but intact. Hair was found in the stomachs of only 2 rats and therefore was not regarded as the primary cause of the lesions. Pappenheimer and Larimore's failure to prevent the lesions with Osborne and Wakeman's yeast extract was regarded as due to the lack of something which is present in whole yeast. Their explanation of the apparently conflicting views of the role of vitamin A deficiency was that Wolbach and Howe had previously observed no gastric lesions in rats on a diet deficient only in vitamin A. Since anorexia is a prominent symptom in vitamin A deficiency, secondary deficiencies are likely to develop. Howes and Vivier believed these secondary deficiencies to be a factor in the appearance of the lesions.

Comment: A review of the gastric lesions present in animals on various deficient diets, particularly those in the forestomachs of rats, does not disclose sufficient evidence to warrant the conclusion that they are definitely malignant. There is a striking similarity between the forestomach changes in rats on deficient diets and those observed in rats with nematode infections. This resemblance is so close that it has been suggested a dietary deficiency is the primary cause of the parasitic tumors. Whether a specific deficiency is responsible for the lesions is still a controversial matter. Cramer [15] suggested a possible mechanism by which dietary deficiencies may lead to papillomatosis of the forestomach. He reviewed the conflicting evidence of its cause appearing in the literature and the highly inconsistent results in his own experiments, previously mentioned. Although different strains of animals vary in their reaction to the same deficiency, this may not adequately account for all observations. The fact that some cutaneous papillomas can be transmitted by means of a virus led Cramer to speculate that the primary cause of papillomatosis of the forestomach may possibly be a virus whose action is enhanced in rats fed a deficient diet. This hypothesis in one form or another has been previously suggested by others, but Cramer's experiments are an example of its possibility and might explain, among other things, the suspected occasional endemic occurrence of forestomach papillomatosis in rats.

Lesions of the glandular stomach have observed in rats on deficient diets [27] but much less commonly than those of the forestomach and they have not been regarded as malignant.

A question of prime importance in relation to gastric lesions resulting from dietary deficiencies of one sort or another is that of the reversibility of the changes. This possibility has not been satisfactorily eliminated in the more severe lesions sometimes regarded as malignant. It seems essential to determine whether the gastric changes will persist and progress invasively after the resumption of a complete diet. The evidence presented by Hoelzel and Da Costa [23b] indicates that the lesions they observed, possibly not as severe but apparently of the same type as those sometimes simulating malignant growth, are reversible.

Carcinogenic Agents.—1. Tar. With the advent of tar as a carcinogenic agent, attention was directed primarily to experimental tumors in organs or tissues other

than the stomach, although some attempts to produce gastric carcinoma with tar have been reported. Ishibashi and Ohtani [28] found definite adenomas, not regarded as malignant, fifty days after the injection of tar into the submucosa of the stomach in rabbits.

Buschke and Langer [29] noted forestomach lesions in 50 of 54 rats after rectal injections of tar once to twice a week for four to six months. The animals were 3 to 5 months old at the beginning of the experiment. The first rectal injection led to rather severe general reactions, although subsequent injections were well tolerated for the next two to three months, and then there was a progressive decline in general health. The animals were allowed to die spontaneously. The lesions were limited to the forestomach and were usually near the ridge separating it from the glandular chamber. The rectum, glandular stomach and intestine showed no significant changes. An excellent description and photographs of the lesions bear out the close resemblance, as pointed out by the authors, to those noted by Fibiger. The changes consisted essentially of ulceration, hyperkeratosis and papillomatosis of the mucosa with a downgrowth of the epithelium, sometimes extending through the muscularis mucosae into the submucosa and part of the muscularis but never through the serosa. Mitotic figures were common. The careful pathologic analysis of the lesions is noteworthy. Although some regional lymph nodes were enlarged, no metastatic tissue was found microscopically nor were metastases found elsewhere. Nest of epithelium sometimes appeared to be isolated, but a connection with the surface epithelium was found. This was not always obvious, and the authors pointed out that the connection might easily have been overlooked in some sections. In addition, the epithelial downgrowths did not seem to infiltrate the deeper structures but rather to push through them, even to the extent of giving the external surface of the stomach a nodular appearance. In view of these observations the lesions were not considered malignant, although the possibility that in time a malignant change might have occurred was discussed. The relation of the rectal injections of tar to the lesions of the forestomach is of considerable interest. Buschke and Langer considered but dismissed the possibility that some tar was swallowed. No gastric parasites were found. They felt the changes were due to the general effect of absorbed tar. In retrospect it may be questioned whether the tar had any specific effect. The animals were allowed to die spontaneously and were reported to have been in a poor nutritional state for some time before death. Presumably there was anorexia with consequent inadequate intake of food and dietary deficiencies such as have been found to lead to similar alterations in the stomach.

Bonne,[9b] in an excellent paper dealing in part with gastric lesions in tarred animals, found benign papillomas in the forestomachs of a few mice. Bonne thought these were probably caused by swallowed tar. When tar was applied to the mouths of 50 mice, the incidence of papillomas definitely increased, and 1 mouse was reported to have had a squamous cell carcinoma of the forestomach. Tar had been applied orally twice a week for thirty-three weeks and then discontinued. At the time of death, one year after tarring was started, this mouse had a carcinoma of the lower lip and buccal mucosa in addition to the gastric tumor, which penetrated the muscularis mucosae and infiltrated almost to the serosa. No metastasis was found. No

[28] *Ishibashi, M., and Ohtani, S.: Gann 15:2, 1921.*
[29] *Buschke, A., and Langer, E.: Ztschr. f. Krebsforsch. 21: 1, 1923.*

further description or illustration of this tumor is given. No malignant gastric lesion was found in 20 rats repeatedly tarred by mouth. A papilloma in the forestomach of 1 rat and some benign changes in the glandular stomach of another were regarded as spontaneous, since similar lesions had been observed in untarred rats. A third rat tarred by mouth twice a week for twenty weeks was found to have bronchopneumonia and two grossly visible white nodules in the lung. Microscopic examination disclosed a large keratinized mass in the periphery of the lung. Squamous epithelium was recognizable at the borders of this mass, which was nowhere seen to be related to a bronchus. The remainder of the lung could not be examined for further squamous cell metaplasia. This finding is interesting, since no squamous cell tumor was found elsewhere to suggest a metastatic lesion in the lung. A photomicrograph beautifully illustrates the keratinized pulmonary mass.

Voronoff and Alexandrescu[30] fed 10 white rats a mixture of tar, hydrous wool fat, aniline oil and toluylenediamine three to four times a week. A peritoneal sarcoma and an adenocarcinoma of the prepyloric portion of the stomach were reported in a rat dying six months later. The latter tumor is described as infiltrating all layers of the stomach, with metastases to the liver and retropyloric lymph nodes. Drawings of the microscopic appearance of this lesion show the superficial gastric mucosa, not including the muscularis mucosae nor the deeper layers of the stomach. Some mucosal ulceration and various alterations of the glandular structure are evident, but the drawings are not clear enough to permit an objective interpretation. There is no illustration of a metastasis. This work apparently has not been repeated by the same or other investigators.

Tani[31] noted marked papillomatosis of the forestomach in a few rats given tar orally. The changes were severe enough to suggest a malignant process. Injections of tar into the gastric wall were found to be less effective. Microscopic studies were not found in the reports available.

Twort and Twort[32a] in a detailed report of lesions found in 60,000 tarred mice, state that while they were not primarily interested in the alimentary tracts of their animals and hence may have overlooked some gastric lesions, they noted occasional papillomas of the forestomach, more frequently in those mice painted with tar for many weeks than in those painted for only a short time. One mouse had a pronounced benign adenomatous or hyperplastic condition of the glandular portion of the stomach. It was, of course, impossible to say whether 1 glandular lesion in 60,000 mice was casually related to the tarring or to the swallowed tar. They found no gastric carcinoma in any of the 60,000 mice.

Mercier and Gosselin[33] injected coal tar in olive oil intraperitoneally into a mouse, which died four months later. A tumor the size of a large pea was found in the forestomach near the limiting ridge. It is briefly described as infiltrating the musculature. The tumor was considered malignant and was regarded as the result of irritation by swallowed hair contaminated with tar rather than of the intraperitoneal injection of coal tar in oil. It is not clear whether metastases were present. There is no illustration.

[30] *Voronoff, S., and Alexandrescu, G.: Néoplasmes 8:129, 1929.*

[31] *Tani, I.: Tr. Jap. Path. Soc. 21: 715, 1931.*

[32] *(a) Twort, J. M., and Twort, C. C.: J. Path. & Bact. 35: 219, 1932. (b) Twort, C. C., and Bottomley, A. C.: Lancet 2: 776, 1932.*

[33] *Mercier, L., and Gosselin, L.: Compt. rend. Soc. de biol. 113: 669, 1933.*

Reinhard and Candee[33a] fed mice 10 mg. of coal tar in butter once a week for seven months and observed no gastric tumors.

2. Carcinogenic Chemicals. With the isolation and synthesis of a carcinogenic constituent of tar and the preparation of many other carcinogenic agents, it became possible to feed animals single chemical compounds of known carcinogenic potency for some tissues and organs. In the meantime the carcinogenic properties of some other substances were recognized or suspected. Some of these have been used in attempts to induce gastric carcinoma in animals, usually by feeding, although other methods have been employed as well.

(*a*) Diaminoazobenzene: Otsuka[34] in 1935 noted papillomatosis of the forestomach in mice fed diaminoazobenzene in olive oil daily. A closely related compound, dimethylaminoazobenzene, has been used in the experimental production of carcinoma of the liver in rats but causes no malignant lesion in the stomach (Kinosita[35]). Diaminoazobenzene, on the other hand, has little effect on the liver. Otsuka observed papillomatosis as early as fifty-nine days after diaminoazobenzene was fed and found that it was present in all mice surviving three hundred and seven days or more. There was no invasion of the muscularis and no metastasis. The changes were considered benign. The glandular stomach was not involved.

(*b*) 1,2,5,6-Dibenzanthracene: Reports of gastric lesions following administration of 1,2,5,6-dibenzanthracene are uncommon.

Perry and Leonard[36] reported that carcinoma of the stomach developed in some mice painted twice a week with 0.3 per cent 1,2,5,6-dibenzanthracene in benzene. In mice painted with theelin in addition to dibenzanthracene more tumors developed, but it is not stated whether this included gastric tumors. It is not clear how long the mice with gastric tumors had been painted. There is no further description. No mention is made of the type of neoplasm—squamous or glandular. There is no illustration of a gastric tumor.

Reinhard and Candee[33a] fed mice 0.02 per cent dibenzanthracene in butter for seven months without obtaining gastric or other tumors.

Ilfield,[37] using Shear's method of incorporating carcinogenic hydrocarbons in cholesterol pellets, implanted 5 per cent dibenzanthracene pellets in the wall of the stomach of a dog. No tumor was found after one year. Similar pellets placed under the gastric serosa of ferrets did not cause a tumor at the time of report, four months later.

Cook and co-workers[38] reported that no carcinoma of the alimentary tract resulted from feeding dibenzanthracene in lard for an unspecified length of time to mice and rats.

Branch[39] painted the skin of mice twice a week with 0.5 per cent dibenzanthracene in benzene and noted considerable licking of the painted areas with the resultant ingestion of dibenzanthracene, but no tumor of the gastrointestinal tract was found in any mouse.

Van Prohaska, Brunschwig and Wilson[40] failed to obtain gastric lesions in white mice by feeding dibenzanthracene in lard three times a week for six months.

Fieser,[41] in a comprehensive review of

[33a] *Reinhard, M. C., and Candee, C. F.: Am. J. Cancer 26: 552, 1936.*
[34] *Otsuka, I.: Gann 29: 209, 1935.*
[35] *Kinosita, R.: Tr. Jap. Path. Soc. 27: 665, 1937.*
[36] *Perry, I., and Leonard, G. L.: Am. J. Cancer 29: 680, 1937.*
[37] *Ilfield, F. W.: Am. J. Cancer 26: 743, 1936.*
[38] *Cook, J. W.; Haslewood, G. A. D.; Hewitt, C. L.; Hieger, I.; Kennaway, E. L., and Mayneord, W. V.: Am. J. Cancer 29: 219, 1937.*
[39] *Branch, C. F.: Am. J. Cancer 26: 110, 1936.*
[40] *Van Prohaska, J.; Brunschwig, A., and Wilson, H.: Arch. Surg. 38: 328, 1939.*
[41] *Fieser, L. F.: Am. J. Cancer 34: 37, 1938.*

the relative carcinogenic properties of various polynuclear aromatic hydrocarbons, found that 1,2,5,6-dibenzanthracene usually requires a longer time to induce skin and subcutaneous tumors in mice and rats than some of the others. The possibility that gastric lesions might result in animals fed dibenzanthracene for longer periods is therefore not entirely excluded.

(*c*) Cholesterol Compounds: Roffo [42a] reported the experimental production of adenocarcinoma of the stomach in rats. All rats were 3 months old at the beginning of the experiment and were maintained on a diet of bread and milk for sixteen to twenty-six months thereafter. A control group of rats fed this diet or bread, milk and unirradiated cholesterol showed no gastric lesions similar to those observed when various additions to the diet were made. The daily additions consisted of 100 mg. of forty-eight hour ultraviolet-irradiated cholesterol, heated cholesterol, sun-treated or ultraviolet-irradiated egg yolk. One group was fed ultraviolet-irradiated bread and milk. In all, 600 rats were used in these experiments. A typical illustration is given in each group, but it is not clear how many rats showed the gastric changes described. Roffo found the most common lesion to be ulceration in various forms and degrees in the glandular stomach and forestomach. The lesions on the glandular stomach are well illustrated. Some were regarded as ulcers in which carcinomatous degeneration had taken place.

In a more recent publication Roffo [42b, c] reported the results of feeding rats various animal fats (beef, pork, or lamb) or olive oil heated to 350 C. for a half hour. This procedure is reported to have changed the cholesterol to oxycholesterin, which was found to have a fluorescence spectrum similar to some of the carcinogenic hydrocarbons. In other respects the experimental method was identical to that of the previous experiment. Malignant lesions of the stomach, liver and lung are described. Lesions of the glandular stomach far outnumbered all others, and the discussion will be limited to these. The gross findings in 200 rats are tabulated and show that over one third had some gastric lesion, most commonly multiple ulcers of the glandular stomach. In some rats gastric tumors (or polyposis) were present. Histologically, in addition to the ulcers, hyperplasia of the gastric mucosa, epithelial cysts (cystadenomas) and atypical glandular epithelium were described, and in some instances destruction of parts of the muscularis mucosae and of the muscularis was present. These changes are well shown in numerous photographs of gross specimens and in photomicrographs. Some of the more advanced lesions were regarded as adenocarcinomas.

Roffo used a total of 1,600 rats in cholesterol feeding experiments of one type or another. The number of lesions regarded as carcinomatous degeneration of ulcers or adenocarcinomas is not entirely clear, but certainly there were quite a few, and control experiments eliminated the possibility that these were coincidental. On the basis of the changes shown in the photomicrographs, the question may be seriously raised as to whether these lesions were really malignant. Aside from the profound changes in the glandular epithelium, some of the strongest evidence in favor of malignancy is found in the fact that in some cases the muscularis was destroyed in places by a downgrowth of atypical glandular tissue, cystadenomatous in form. The question arises whether a process limited in all cases by the gastric serosa can be considered malignant. In the absence of any mention of a metastasis from a gastric

[42] *Roffo, A. H.:* (*a*) *Ztschr. f. Krebsforsch. 47: 473, 1938;* (*b*) *Bull. Assoc. franç. p. l'étude du cancer 28: 556, 1939;* (c) *Bol. Inst. de med. exper. para el estud. y trat. d. cáncer 15: 407, 1938.*

lesion or of an instance of invasion of a neighboring structure or organ, the evidence for malignancy is not entirely convincing. In this connection it is interesting to compare the photomicrographs of lesions regarded as adenocarcinomas by Roffo with the less severe but similar changes observed by Bullock and Rohdenburg [16] in rats after introducing into the stomachs cork balls with protruding pinpoints.

Waterman [43] fed tarred mice cholesterol oleate twice a week. The mortality was high. Forty mice survived sixty days or more. Twelve of these had benign forestomach papillomas, and 3 had what was interpreted as squamous cell carcinoma of the forestomach. The latter were found in mice that succumbed ninety-three, two hundred and forty-eight and two hundred and forty-eight days, respectively, after the feeding of cholesterol oleate. No further description is given. Metastases are not mentioned; presumably there were none. A low power photomicrograph illustrating a carcinoma shows a papilloma near the limiting ridge. No invasion of the muscularis can be seen. On the basis of this illustration it is difficult to differentiate the lesion from previously described benign papillomas. Waterman in another experiment fed 6 untarred mice cholesterol oleate three times a week. After three hundred and eighteen days he found a malignant papilloma in the forestomach and a fibrosarcoma in the neck of the stomach in 1 mouse. Another had a squamous cell carcinoma of the forestomach after four hundred and forty-one days. A third mouse had polypoid growths in the glandular stomach showing many mitoses after three hundred and sixty days. No metastases are mentioned, and no description of the lesions are given, although photographs of the gross and microscopic appearance accompany the report. These photographs are in no way convincing. A fourth mouse after four hundred and forty-one days was found to have a lesion regarded by Waterman as an early adenocarcinoma of the stomach without a metastasis. This is a most interesting interpretation. A description and illustrations of the lesion are given. It appears to be along the limiting ridge, depressed in relation to the surrounding mucosa, and might easily be overlooked on gross examination. The muscularis mucosae is not distinct. There is no invasion of the muscalaris. A higher power photomicrograph taken from an unspecified part of the mucosa shows an acinar arrangement of apparently single layers of cells. The description and illustrations indicate there was some alteration in a small part of the glandular mucosa. That this represented a malignant change is, however, a matter of opinion not well supported by the evidence.

(*d*) 3,4-Benzpyrene: Oberling, Sannie, Guérin and Guérin [44] fed 20 mice 3,4-benzpyrene in lard once a week. Sixteen mice succumbed at the end of six months. One of these showed benign hyperplasia of the forestomach mucosa. None of the others had any appreciable gastric changes. Of 20 rats fed benzpyrene in lard, 10 died within seven months. None of these had any significant gastric lesion. The other 10 rats appeared in good health at the time of the report.

Ilfield [37] obtained negative results (at four months) by implanting 5 per cent benzpyrene in cholesterol pellets under the gastric serosa of ferrets.

Waterman [43] fed 6 mice 0.4 per cent 3,4-benzpyrene in lard daily for periods ranging from one hundred and twelve to

[43] *Waterman, N.: Acta cancrol. 2: 375, 1936.*

[44] *Oberling, C.; Sannie, C.; Guérin, M., and Guérin, P.: Bull. Assoc. franç. p. l'etude du cancer 25: 156, 1936.*

three hundred and thirty-six days. When benzpyrene was given in watery colloidal solution, no gastric lesions were observed. With lard as the solvent, however, 5 mice had forestomach tumors that were regarded as squamous cell carcinoma. Metastases to the portal glands, peritoneum, liver, spleen or lungs were reported in 4 of these animals, but the several photographs of the lesions, including one of a reported metastatic nodule in the liver, are not convincing, and no microscopic description of the primary or metastatic lesions is given.

Rusch, Baumann, and Maison [45] reported a low grade adenocarcinoma of the stomach in 1 of 5 rats fifteen months after injection of 3,4-benzpyrene into the submucosa of the pyloric area. A tumor, 1 by 1 cm., which had invaded the muscularis was found. There were no metastases. No further description or illustration is given. A myoma and a spindle cell sarcoma were found in 2 of the other rats.

(*e*) Methylcholanthrene: Van Prohaska, Brunschwig and Wilson [40] gave 15 mice 2 minims (0.12 cc.) of a 1 per cent solution of methylcholanthrene in olive oil orally three times a week. Eight mice survived for six months and were killed when they appeared weak and emaciated. Two of these had benign squamous cell papilloma of the forestomach at the end of one hundred and sixty-four and one hundred and seventy-five days, respectively. Four of the others had squamous cell carcinoma of the buccal mucosa or of the skin about the mouth. When a 1 per cent solution of methylcholanthrene in lard was injected into the mouths of 33 mice every other day for four months, no benign or malignant gastric lesion was found. One mouse had a squamous cell carcinoma of the angle of the mouth after sixty-seven days and another a hypopharyngeal squamous cell carcinoma after one hundred and forty days. These authors pointed out the close relationship of methylcholanthrene to the bile acids which normally bathe a large portion of the gastrointestinal tract. They conclude, however, that methylcholanthrene administered orally does not have a marked carcinogenic effect on the alimentary canal even in the upper portion, lined by squamous epithelium. They suggest that certain mechanical factors may explain this in part. in addition to an apparent high degree of resistance of the epithelium of the stomach and intestine. On cutaneous application and subcutaneous injection of carcinogens, prolonged contact with the cells is possible, whereas in the alimentary canal the mucosa is constantly washed by various fluids and is, moreover, covered and perhaps protected by a layer of mucus.

Necheles [46] injected 250 mg. of methylcholanthrene into the submucosa of the anterior wall of the stomach near the proximal border of the antrum in a dog. Three gastric biopsies taken in the region of the injection over a period of nine months have shown an inflammatory reaction but no evidence of malignant change. The experiment is still in progress.

Stewart [5b] reported squamous papilloma of the stomach in 4 and squamous cell carcinoma of the stomach in 4 of 30 strain A male mice which when 3 months old received injections of a solution of methylcholanthrene in mineral oil into the anterior wall of either the glandular stomach or the forestomach. All the tumors were forestomach lesions and are excellently described and illustrated. The four carcinomas were visible; one was adherent to the liver. They were located in the an-

[45] *Rusch, H. P.; Bauman, C. A., and Maison, G. L.: Arch. Path. 29: 8, 1940.*

[46] *Necheles, H.: Personal communication to the authors.*

terior wall except one, which was some little distance from the point of injection, at the posterior inferior margin of the forestomach. Microscopically, the infiltrating epithelium invaded all layers of the stomach and was composed of basal cells, prickle cells and flat squamous cells, atypical in size, shape and staining. There were numerous mitotic figures. In one tumor there were nests of epithelium within thin-walled vessels, either lymph vessels or blood vessels, between the two muscle layers of the stomach. In the case in which the abscessed liver was adherent to the wall of the stomach opposite the tumor, masses of keratin were observed within the abscess. In 2 cases small nodules composed of tumor cells were adherent to the external surface of the peritoneum. One tumor was successfully transplanted to 4 of 6 strain A mice, which had large tumors at the sites of inoculation after three weeks. Transplants of these in turn were successful in 2 of 6 mice, which had large tumors after one month. The tumors developing from the transplants were identical in morphologic characteristics to the original tumor of the stomach. In the literature on successfully induced squamous cell carcinoma of the stomach, this is one of the few reports accompanied by clear pathologic descriptions, sufficient relevant details, and photomicrographs to show the significant changes.

Stewart has indirectly raised several points of interest. Invasion of the muscularis was taken as the criterion to differentiate carcinoma from papilloma. The absence of such invasion has usually been regarded as one of the chief objections to classifying certain experimental gastric lesions as malignant. Stewart has illustrated such invasion of the muscalaris and the presence of nests of epithelium within thin-walled vessels, either lymph vessels or blood vessels. The latter is usually considered a reliable indication of malignancy in spontaneous tumors. Successful transplantation of gastric tumor tissue has rarely been demonstrated before. These points will be discussed in more detail later. The possibility of coincidence is entirely eliminated by the use of pure strain mice, for no similar tumor has been observed to occur spontaneously in several thousand strain A mice.

3. Miscellaneous Factors. Twort and Bottomley [32b] reported a squamous carcinoma of the forestomach in a mouse painted with a watery solution of a mixture of chrysene ammonium and sodium sulfonite for twenty weeks. The tumor invaded the liver and adjacent organs. Since this was the only mucous membrane tumor in a large number of mice (12,000) subjected to similar procedures, it was considered to be spontaneous.

Hormonal substances have been of considerable importance in some fields of experimental induction of tumors; however, gastric lesions apparently have been rarely found. Pierson [48] reported a growth resembling mammary gland in the wall of the stomach of a castrated rabbit which had received 0.1 mg. of an estrogen twice a week for three years. In the thickened gastric wall were numerous infiltrating tubules and ducts filled with a material staining pink with eosin. This glandular tissue was nowhere seen to be related to the gastric epithelium in serial sections. There was extensive squamous cell metaplasia. This was the only such tumor found in a large group of rabbits receiving the estrogen.

Domagk [49] reported a gastric adenocarcinoma in 1 of 20 mice fed a diet of rice and 20 per cent olive oil, alternating each week

[47] *Footnote deleted.*

[48] *Pierson, H.: Ztschr. f. Krebsforsch. 48: 177, 1938.*

[49] *Domagk, G.: Ztschr. f. Krebsforsch. 48: 283, 1938.*

with the usual diet, for one year. The tumor was visible grossly. Microscopically, it consisted of atypical glandular epithelium with numerous mitotic figures and extended through the muscularis mucosae and the muscularis but was limited by the serosa. There were associated inflammatory changes in the gastric wall. No metastasis is mentioned. Photomicrographs of this tumor show the changes described. Gastric polyposis, regarded as precancerous, was found in some of the other mice. A pulmonary nodule in 1 mouse was interpreted to be a metastasis from the stomach, although the gastric lesion was apparently considered precancerous. There is no photograph or description of the pulmonary nodule. No similar gastric lesion was found in 20 mice that were not fed olive oil.

COMMENT

Nomenclature.—The term "experimental gastric carcinoma" almost always refers to squamous cell carcinoma of the forestomach. In a sense this is confusing, since carcinoma of the stomach in man implies adenocarcinoma. There is no experimental evidence to suggest that the two types are related except in the anatomic location of both in the stomach. Occasionally the term "experimental gastric carcinoma" has been applied to malignant tumors of other organs transplanted to the gastric wall. The use of the phrase in this sense is misleading.[50]

Sarcoma.—Reports of experimental sarcoma of the stomach are uncommon and have not been included in this review. Brunschwig [51] found large fibrosarcomas in 2 of 3 male rats exposed for an indeterminate length of time to various carcinogenic agents. Each of these animals also had a benign fibroadenoma of the breast.

Adenocarcinoma.—There are in the literature relatively few claims [52] of the production of experimental adenocarcinoma of the stomach. On close scrutiny these reports either are not convincing or do not permit objective evaluation of the malignant nature of the changes. There is no well established case of adenocarcinoma of the stomach resulting from an experimental procedure.

The fact that attempts to induce adenocarcinoma of the stomach with known carcinogenic agents have been unsuccessful raises several considerations.

1. Time Factor. The induction period may be considerably longer than for other experimental cancers.

2. Mechanical Factors. Van Prohaska, Brunschwig and Wilson [40] called attention to the problem of keeping the carcinogenic agent in the stomach and, even when this is accomplished, of bringing the agent into intimate contact with the secreting gastric mucosa covered with mucus. The implantation or injection of carcinogenic compounds into the wall of the glandular stomach eliminates some of the mechanical difficulties, but these methods have not yet yielded the positive results that might be expected. Although these procedures may be of considerable value, particularly in the selection of effective carcinogens, feeding experiments perhaps have the advantage of being more physiologic.

3. Chemical Factors. Perhaps there is a carcinogenic agent, specific for the glandular tissue of the stomach. Although this is purely speculative, there is some basis for such a possibility. Shear's [53] studies in pure strain mice indicate that 2-amino-5-azotoluene is a specific carcinogenic com-

[50] *Besredka, A., and Gross, L.: Ann. Inst. Pasteur 62: 253, 1939; abstracted. Am. J. Cancer 37: 124, 1939.*

[51] *Brunschwig, A.: Personal communication to the authors.*

[52] *Voronoff and Alexandrescu.*[30] *Roffo.*[42] *Waterman.*[43] *Rusch and others.*[45] *Domagk.*[49]

[53] *Shear, M. J.: Am. J. Cancer 29: 269, 1937.*

pound for liver tissue. Methylcholanthrene, which is closely related to bile acids, appeared on theoretic grounds to be possibly carcinogenic for gastric glandular tissue. Reports, however, do not yet indicate that it has such an action when given by mouth (Van Prohaska, Brunschwig and Wilson [40]) or when injected into the gastric wall (Stewart [5b]).

4. Species or Strain Susceptibility. Experimental cancer may at times be induced in an organ or tissue of an animal while the same procedure in other animals of a closely related species or strain has no carcinogenic effect. The well known difference in the response of rats and rabbits to tarring is a classic example. Relatively few species have been used in attempts to induce gastric adenocarcinoma. The possibility that a species or strain susceptible to known carcinogenic agents may exist is not entirely excluded.

5. Tissue Resistance. A more basic factor may be the apparent resistance of normal gastric glandular tissue to a carcinomatous change. There is considerable pathologic evidence that carcinoma does not develop in an unaltered gastric mucosa (Konjetzny [7]). The question arises as to whether the known carcinogenic agents can be effective in the normal glandular stomach of an animal. Possibly preliminary benign changes are prerequisite. The more important question would then still remain as to what brings about the earlier benign changes.

Squamous Cell Carcinoma.—It is generally accepted that squamous cell carcinoma of the forestomach has been experimentally produced in rats and mice. However, the impression given at times that it has been produced rather commonly is not supported by a review of the literature. The actual number of instances on record is difficult to estimate in view of the doubtful malignancy of some induced forestomach tumors regarded as carcinoma and the questionable relation of some of these to the experimental procedure. In this regard Stewart's [5 6] work gives promise of more successful and consistent results in the near future. One of his observations is particularly noteworthy: With methylcholanthrene the estimated average induction period of both benign and malignant squamous cell tumors of the stomach was about fourteen months. This is a considerably longer period than is needed to induce tumors of other tissues with methylcholanthrene in the same strain of mice. Although this apparently greater resistance of gastric squamous epithelium to carcinogenic action is not definitely known to exist in all animals and for all carcinogenic compounds, the numerous megative results obtained in experiments of shorter duration strongly suggest this possibility.

In weighing the evidence of malignancy, the presence of a mass of atypical or keratinized squamous cell tissue or of a large cavity filled with caseous material in the lung of rats usually does not indicate a metastasis. It is frequently found that not much significance can be attached to it. Bullock and Rohdenburg [16] called attention to this fact in 1918 and in an accompanying photomicrograph showed squamous cell epithelium with mitotic figures in the lung of a rat with bronchopneumonia. Bonne [9b] later found a large keratinized squamous mass in the periphery of the lung of a rat dying of bronchopneumonia. No connection with a bronchus could be found. There was no squamous cell tumor elsewhere, and it was interpreted to be a metaplastic mass primary in the lung. Wolbach and Howe [21] and others found widespread squamous cell metaplasia in vitamin A–deficient rats. None, however, have shown the presence of squamous cell meta-

plasia and bronchiectasis in rats as convincingly as Passey, Leese and Knox.[13c] These workers found that 51 per cent of a large group of laboratory rats had bronchiectasis in some degree or other, which occurred independent of the diet. Some bronchiectatic cavities filled with purulent material replaced several lobes of the lung. Squamous cell metaplasia of the bronchial tree was also common and independent of the diet, although it was more marked in vitamin A–deficient rats. Keratinization of these metaplastic masses was almost exclusively limited to the vitamin A–deficient animals. In 1 rat and 2 mice squamous cell metaplasia of the alveoli was found. These lesions are excellently illustrated. There is no photomicrograph in the literature of a so-called metastasis to the lung from a squamous cell tumor of the forestomach that cannot be matched among those accompanying the paper of Passey, Leese, and Knox. Theseau thors considered the possibility of several etiologic factors without reaching a definite conclusion. It is certain, however, the lesions are not metastases. This is confirmed by many unpublished observations (Steiner [54]).

Abdominal metastases have apparently not been so confusing. Enlarged abdominal lymph nodes obviously do not indicate metastasis in all cases. In the presence of severely infected benign forestomach changes, it might be surprising if the regional lymph glands were not enlarged. For this reason illustrations of such enlargements are not convincing unless accompanied by photomicrographs showing the metastatic tissue. Likewise there are causes other than carcinomatous invasion of neighboring structures to account for adhesions between the stomach and these organs.

[54] *Steiner, P. E.: Personal communication to the authors.*

Evidence in favor of malignancy could be shown by irreversibility of experimental gastric lesions simulating carcinoma. Obviously it is not always possible to demonstrate this, especially when the carcinogenic agents are injected into the gastric wall. In the case of dietary deficiencies or the feeding of carcinogenic agents this method seems applicable. Bonne's[9b] report of a squamous cell carcinoma in a mouse which had received tar by mouth for thirty-three weeks and which died almost five months later shows that the method is feasible. Another example is the experiment of Hoelzel and DaCosta[23b] in which they used dietary means to induce forestomach lesions in rats, which almost disappeared when a complete diet was resumed.

Transplantation of squamous cell tumors of the forestomach has not been attended by much success. This may have been due to (1) infection of the implants, as Fibiger and others have emphasized, (2) the nonmalignant nature of some of the tumors, (3) the large amount of acellular and keratinized material present or (4) the difficulties in transplanting tissue from one strain of animals to another. Fibiger[14c] apparently succeeded in the case of a mouse. Metastases to lymph nodes were transplanted into 28 of 55 mice that survived inoculation, representing four generations of "takes" covering a period of one year. The transplanted tissue maintained the histologic appearance of the original tumor of the stomach. Slye, Holmes and Wells[4] in the case of two spontaneous gastric carcinomas in mice obtained only a few takes with one of the tumors, which could not be carried to a second generation. Stewart[5b] transplanted an induced squamous cell tumor of the stomach of a mouse through two generations. Microscopically, the transplants were identical to the original tumor.

In this connection the experience with transplantation of induced squamous cell tumors of the skin deserves consideration. Woglom[55] in a comprehensive review of experimental tar cancer stated that spontaneous keratinizing neoplasms had long been known to be refractory to propagation and that similar difficulties were encountered with induced squamous cell tumors even when they gave definite evidence of being malignant in other ways. The failure to obtain "takes" with such tumors cannot, therefore, be regarded as eliminating the possibility of malignancy. On the other hand, a positive result might be due merely to temporary proliferation of the grafts. In either case the result might be equivocal. Murray and Woglom (cited by Woglom[55]) found autotransplants in mice more satisfactory than homotransplants. Normal tissues or benign growths proliferated only temporarily or not at all, whereas malignant growths gave a high percentage of positive results. In the hands of these observers autotransplantation was sometimes successful with tar tumors that appeared histologically benign at the time of implantation. This was regarded as evidence that autotransplantation could at times facilitate the recognition of a malignant tumor before histologic examination. Kreyberg[56] was unable to confirm the observation that tumors appearing histologically benign in mice were autotransplantable.

Rous and Kidd[57] noted that autotransplants of a virus papilloma in rabbits in some instances grew while the original papilloma retrogressed. This was found particularly when inflammation of bacterial origin ensued at the site of inoculation.

These examples illustrate the difficulties encountered in interpreting the significance of both successful and unsuccessful transplants of induced squamous cell tumors of the skin. Since these experimental tumors are the ones most analogous to those of the forestomach, the same uncertain interpretation may apply to the results of transplantation of the latter as well.

Criteria of Malignancy.—The question of what characterizes an experimental carcinoma has been a source of controversy. Fibiger[14c] set down clearly his criteria of malignancy with respect to squamous cell tumors of the forestomach and supported his opinion by pointing out the similarity of such changes to those occurring in spontaneous squamous cell carcinoma in man and animals. These criteria were:

1. Heterotopic downgrowth of epithelial cells, not only the normal type of the basal epithelial layers, but, mixed with these, atypical and keratinized cells in abundance, partly arranged as spherical masses and horny globes.

2. Infiltrative growth of these heterotopic and atypical epithelial cells into the deeper layers, splitting up invasively the elements of the connective tissue of the mucosa and the muscle cells of the muscularis mucosae, forming isles and spurs in the latter—as most frequently seen—also penetrating through this membrane into the superficial or deeper layers of the submucosa.

Bullock and Rohdenburg[16] questioned the malignant nature of Spiroptera tumors such as Fibiger's in the absence of active invasion of the muscularis and definite metastases. Bonne placed considerable reliance on invasion of blood vessels as a sign of malignancy in 1 case[9a] and infiltration of the muscularis in another.[9b] Stewart[5b] differentiated papilloma from carcinoma on the basis of invasion of the outer muscular layers of the stomach. Additional evidence of malignancy was also present in one case in which nests of epithelium were found in thin-walled vessels between the muscle layers of the

[55] *Woglom, W. H.: Arch. Path. 2: 533 and 709, 1926.*
[56] *Kreyberg, L.: J. Cancer Research 9:381, 1925.*
[57] *Rous, P., and Kidd, J. G.: J. Exper. Med. 69: 399, 1939.*

stomach, either lymph vessels or blood vessels; and in another the tumor was successfully transplanted to other mice through two generations.

A fundamental question is whether the microscopic criteria of spontaneous malignancy can be applied to experimental tumors in differentiating the malignant from the benign. In the final analysis, malignancy may be judged only by the course of events. Certain histologic characteristics of spontaneous lesions have become synonymous with malignancy; however, this relationship was at first empirically established. Tumors following a malignant course were found to have some differentiating morphologic characteristics. Earlier and earlier stages of these characteristics were recognized, so that now it is often possible to predict that a spontaneous tumor will follow a malignant course on the basis of its structure only and without any definite proof of malignant activity beyond a few microscopic changes which, if they did not progress, could not be classified as malignant and would not interfere with the well-being of the organism. If early morphologic changes from the accepted normal are used to predict a malignant sequence, they are reliable guides only so far as this sequence has been shown always to follow. It cannot be inferred with certainty that the histologic criteria established empirically as pointing to an irreversible and progressive process in a spontaneous tumor necessarily apply to induced tumors or other forms of spontaneous tumors. If a malignant alteration represents an intrinsic irreversible cellular change, manifested by aggressive and destructive invasion of other tissues and organs and continuing until the death of the organism, some of the criteria of malignancy applied to induced tumors may at times be inadequate.

These remarks in relation to experimental squamous cell carcinoma of the forestomach can become the subject of futile controversy. However, if detailed and careful studies of induced squamous cell tumors of the skin, such as those of Yamagiwa and Ichikawa [58] and Ichikawa and Baum [59] and the comprehensive reviews of Woglom [55] and Seelig and Cooper,[60] are again consulted, some light may be thrown on the problem.

Murray and Woglom (cited by Woglom [55]) made use of four criteria of malignancy: "(1) the progressive growth of a tumor after painting has been discontinued, and the growth of its autotransplants; (2) the recurrence after wide excision; (3) histologic evidence of local infiltrative growth, and (4) metastases. They regarded the loss of differentiation and the presence of atypical cellular characteristics as wholly inadequate." These investigators apparently found that simpler criteria of induced malignancy did not distinguish benign from malignant tumors.

Rous and Kidd [57] described squamous cell tumors in rabbits following repeated tarring of the ear which have all the morphologic appearances of carcinoma, including extension through lacunae in the cartilage and presence of proliferating epithelium in the lymphatics. These tumors were at times morphologically indistinguishable from carcinoma and were called carcinoids. When the tarring was discontinued, the carcinoids retrogressed whereas the carcinomas continued to show active invasive properties. If the tarring was continued without interruption, the carcinoids eventually ceased to grow destructively and took on the gross forms

[58] *Yamagiwa, K., and Ichikawa, K.; J. Cancer Research 3: 1, 1918.*

[59] *Ichikawa, K., and Baum, S. M.: J. Cancer Research 9: 85, 1925.*

[60] *Seelig, M. G., and Cooper, Z. K.: Am. J. Cancer 17: 589, 1933.*

of old papillomas. These investigators also mentioned a group of tumors which had active malignant properties only as long as tarring was continued.

On the basis of these and numerous similar observations in regard to experimental squamous cell tumors of the skin it is questionable whether the morphologic characteristics of spontaneous squamous cell carcinoma in man or animals can be applied to induced gastric tumors unless *the latter continue to show malignant activities in the absence of the agent used to bring them about*. Fibiger believed he demonstrated such an irreversible change, but the factor of a dietary deficiency was not eliminated in his experiments. Since some dietary deficiencies in themselves apparently lead to forestomach changes meeting Fibiger's criteria of malignancy, the validity of his interpretation is open to question. In view of this there is obviously some hesitancy in agreeing that all experimental squamous cell tumors of the forestomach regarded in the literature as carcinoma do actually represent maligant alteration of tissues.

What criteria would serve to differentiate induced benign and malignant gastric tumors cannot be settled at present. More of these tumors will have to be observed carefully in order to determine their own peculiarities. It is not known, for example, whether such carcinomas are more apt to metastasize than they are to invade neighboring organs; or whether invasion of the muscularis indicates a definitely irreversible process. Induced cancers should, however, have those characteristics generally considered inherent in a malignant growth: (1) the ability to proliferate independently as metastases; (2) the ability to invade progressively and destructively neighboring tissues and organs; (3) irreversibility of these properties in the absence of the extrinsic factor initially held responsible for the cellular change. Since such changes have been observed to occur in spontaneous squamous cell carcinoma of the forestomach in mice (Slye, Holmes, and Wells;[4] Wells, Slye, and Holmes[3]) there should be, in addition, (4) reasonable evidence to indicate a causal relation of the experimental procedure to the tumor.

Application of these criteria to induced gastric tumors is not always easy, but unless they can be demonstrated, the malignant nature of the tumor cannot be considered as proved. The histologic appearance of the tumor alone is not adequate.

SUMMARY

Spontaneous gastric adenocarcinoma is found rarely in animals and for all practical purposes can be said to occur exclusively in man. Consequently studies of this most important human malignant lesion are limited for the present to clinical material. A review of the literature discloses no reliable method of inducing adenocarcinoma of the stomach in animals; in fact, there is no well established case of an adenocarcinoma of the stomach produced experimentally.

Some success has attended efforts to induce squamous cell carcinoma of the forestomach in mice and rats, although considerably less than the claims in the literature would indicate. There is no experimental evidence to suggest that the two types of gastric carcinoma are related except in the anatomic location of both in the stomach.

The criteria of induced malignancy are considered. Proof of malignancy is not given by the histologic appearance of a tumor, whether spontaneous or induced, but by the demonstration of malignant activity as evidenced by: (1) the ability to proliferate independently as metastases; (2) the ability to invade progressively and destructively neighboring tissues and or-

gans; (3) irreversibility of these activities, which must be shown to continue in the absence of the extrinsic factor initially held responsible for the cellular changes. It must, furthermore, be shown that (4) a given malignant change occurs with sufficient regularity to establish a causal relationship of the experimental procedure to the cancer.

Drs. Ludvig Hektoen, Paul E. Steiner, and Alexander Brunschwig made helpful suggestions and gave constructive criticism.

ADDENDUM

Lorenz and Stewart (*1*)[d] recently reported squamous-cell carcinoma of the forestomach in mice given orally an aqueous olive-oil or mineral-oil emulsion containing either 20-methylcholanthrene or 1,2,5,6-dibenzanthracene instead of drinking water. All 40 mice which had come to autopsy up to the time of the preliminary report (experiment in progress 7 months) had lesions of the mucosa of the fore stomach, and of these 10 had squamous-cell carcinomas. The latter have so far occurred in strain A and strain A backcross mice which were given methylcholanthrene emulsions. Four strains of mice are being used in this experiment. It is of interest that 13 of the 40 mice had adenocarcinoma of the small intestine.

Lorenz and Stewart described the lesions found in mice with squamous-cell carcinoma of the forestomach as follows:

> The majority of the stomachs with squamous-cell carcinoma were greatly enlarged, and a palpable mass could be outlined during life in the region of the stomach. The forestomach was enlarged several times, and the pyloric chamber was small. On the serosal surface, there were usually one to several nodules of varying size. In some cases, these nodules extended directly into the spleen, diaphragm, body wall, and pancreas. In several cases there were grayish masses in the mesenteric lymph nodes, and in one case each a small gray nodule in the genital omentum and in the lung. Upon opening the stomach after fixation, the wall of the forestomach was found to be markedly thickened, either diffusely or in localized areas, by grayish-white tissue which in many cases almost completely obliterated the lumen. The mucosa of the pyloric chamber was not involved except in certain cases in which the cardiac mass overhung somewhat the glandular mucosa. Microscopically, all the carcinomas were of the squamous-cell type and showed extensive keratinization. The tumor tissue extended through all coats of the gastric wall, formed nodular masses on the peritoneal surface, and in three cases showed infiltration of, or metastases to the mesentery, pancreas, mesenteric lymph nodes, genital omentum, spleen, diaphragm, lung, chest wall, and posterior abdominal wall.
>
> No case of spontaneous squamous-cell carcinoma of the forestomach in mice of the strains used in these experiments has occurred in this laboratory.

The pathologic changes described are clearly and convincingly shown in numerous photomicrographs and photographs of gross specimens including those cases of squamous-cell carcinoma of the forestomach with extensive extragastric infiltration of, and widespread metastases to the organs and tissues mentioned.

Although experimental carcinoma of the small intestine is outside the scope of this review, it is noteworthy that it has rarely, if ever, been observed before. Lorenz and Stewart (*2*) have reported 13 adenocarcinomas of the small intestine in 10 of 40 strain A and strain A backcross mice, in one of which metastatic deposits were found in a mesenteric lymph node. The mucosa of the pyloric (or glandular) stomach was not primarily involved by carcinoma in any mouse. These adenocarcinomas followed the ingestion of methylcholanthrene and dibenzanthracene administered orally in the same manner

[d] *We are indebted to Dr. Lorenz and Dr. Stewart for making this information available to us while it was in press, together with numerous photomicrographs and photographs of gross specimens showing the gastric lesions described.*

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as to the mice which had squamous-cell carcinoma of the fore stomach. These observations are significant, since heretofore experimental adenocarcinoma of any part of the gastrointestinal tract has been exceedingly rare.

It should be noted that to date Lorenz and Stewart have found that both squamous-cell carcinoma of the forestomach and adenocarcinoma of the small intestine have occurred in the same two strains of mice (strain A and strain A backcross) and that the administration of the same carcinogenic hydrocarbons by the same method has not been followed by these carcinomas in mice of the other strains employed. Strain A mice were also used in Stewart's earlier work (*5b*) in which squamous-cell carcinoma of the forestomach was observed following injection into the gastric wall of methylcholanthrene in mineral oil.

The ingenious, yet simple method devised to give water-insoluble carcinogenic hydrocarbons to mice in the form of an emulsion in place of drinking water merits note.

This work constitutes definite progress in the field of experimental cancer of the digestive tract.

REFERENCES

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(*2*) LORENZ, E., and STEWART, H. L.: Intestinal carcinoma and other lesions in mice following oral administration of 1,2,5,6-dibenzanthracene and 20-methylcholanthrene. J. Nat. Cancer Inst., 1:17-40 (1940).